

ISMP Medication Error Report Analysis

Plain Dextrose 5% in Water or Hypotonic Saline Solutions Could Result in Acute Hyponatremia and Death in Healthy Children

Investigate and Clarify Requests for Missing Doses

Provera, Prozac, or Proscar?

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These medication errors have occurred in health care facilities at least once. They will happen again—perhaps where you work. Through education and alertness of personnel and procedural safeguards, they can be avoided. You should consider publishing accounts of errors in your newsletters and/or presenting them at your inservice training programs.

Your assistance is required to continue this feature. The reports described here were received through the Institute for Safe Medication Practices (ISMP) Medication Errors Reporting Program. Any reports published by ISMP will be anonymous. Comments are also invited; the writers' names will be published if desired. ISMP may be contacted at the address shown below.

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PLAIN D5W OR HYPOTONIC SALINE SOLUTION COULD RESULT IN ACUTE HYONATREMIA AND DEATH IN HEALTHY CHILDREN

ISMP recently learned about the tragic deaths of 2 children stemming from severe postoperative hyponatremia. The fatal events occurred at 2 different hospitals. In at least 1 of these cases, it is clear that the rapid administration of plain dextrose 5% in water (D5W)

postoperatively resulted in acute hyponatremia secondary to free water retention (also called water intoxication, see Hyponatremia and Water Intoxication). Postoperative children are at high risk for developing hyponatremia, and many fatalities from this disorder have been reported in the literature.¹⁻¹⁴ When the serum sodium concentration rapidly falls below 120 mEq/L over 24 to 48 hours—

as in Case 1 and Case 2—the body's compensatory mechanism is often overwhelmed and severe cerebral edema ensues, resulting in brainstem herniation, mechanical compression of vital midbrain structures, and death.¹⁵

Case 1

In the first case, the child underwent an outpatient tonsillectomy and adenoidectomy. Postoperative orders included intravenous (IV) fluids of "1000 cc D5W – 600 cc q8h." An experienced pharmacist accidentally calculated the infusion rate incorrectly and entered 200 mL/h instead of 75 mL/h on the child's electronic medication administration record (eMAR). He used a calculator and performed the calculation twice but had set up the mathematical problem incorrectly. Thinking in terms of how many 600 mL "doses" would be needed, he set up the calculation as follows: 600 mL (the volume to infuse over 8 hours) divided by 3 (the number of 600 mL "doses" he thought would be needed for 24

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hours) and arrived at a 200 mL/h infusion rate.

The nurse who started the infusion did not detect the pharmacist's error. She had quickly looked at the surgeon's postoperative orders and had obtained a bag of D5W to hang. The nurse felt rushed by the hectic pace of the unit and was distracted during the verification process because she had to find an infusion pump to administer the IV solution. She thought her memory of the written order was sufficient for verification of the pharmacist's entry on the eMAR. This was not her usual practice; however, like other nurses on the unit, she had come to rely on the accuracy of their pharmacists who "never made mistakes." When the first 1,000 mL bag of D5W was empty, the nurse hung a second bag to infuse at 200 mL/h.

Several times throughout the day, the child vomited small amounts of dark, bloody secretions, as expected from the surgery. Near the anticipated time of discharge that afternoon, the child's mother asked a nurse to administer an antiemetic before she took her daughter home. About 40 minutes after receiving promethazine 12.5 mg IV, the child became lethargic and began experiencing jerking movements, rigid extremities, and rolled-back eyes. The surgeon attributed this to a dystonic reaction from promethazine, administered a dose of IV diphenhydramine, and admitted the child to a medical-surgical unit.

During the next few hours, the child's vomiting worsened, she became more unresponsive, and the seizure-like activity became much more pronounced and frequent. The nurses called the child's surgeon multiple times to report the seizure-like activity, during which additional doses of IV diphenhydramine were prescribed and

subsequently administered. Several nurses also told the surgeon that the seizure-like activity appeared to be more than a dystonic reaction to promethazine, although none of the nurses had ever witnessed such a reaction. Unfortunately, during this time the nurses failed to notice the infusion rate error or recognize that an infusion of plain D5W alone or an infusion rate of 200 mL/h was unsafe for a 6-year-old child. Subsequently, a third 1,000 mL bag of D5W was hung after the second bag had infused.

After the child developed significant bradycardia that necessitated calling a code, the surgeon came into the hospital, observed the child having a grand mal seizure, and consulted a pediatrician to help manage the seizures. The consulting pediatrician finally recognized that the child was experiencing hyponatremia and water intoxication due to the erroneous infusion rate of 200 mL/h during the previous 12 hours and the lack of sodium chloride in the infusate. The child had nonreactive pupils and exhibited decerebrate posturing. Stat lab studies showed a critically low concentration of sodium of 107 mEq/L. A computed tomography scan of the brain revealed cerebral edema and, despite treatment, the child subsequently died.

Case 2

In the second case, the child underwent surgery for coarctation of the aorta, a condition that had been identified in the otherwise asymptomatic, healthy child during a school physical. The child's postoperative course seemed to be progressing well, but later, on post-op day 1, his physician prescribed a furosemide infusion (1 mg/h) because the child's urinary output was less than expected, despite several doses of *Edocrin* (ethacrynic acid).

By post-op day 2, the child's serum sodium level had dropped, so his physician prescribed an infusion of sodium chloride. It is uncertain whether the sodium chloride was ever administered because the child's sodium level continued to drop, and administration of the prescribed infusion was never documented on the eMAR.

The child became less responsive throughout the morning of post-op day 2, and his parents expressed concern to several nurses when they could not awaken their son. The nurses assured the parents that deep sleep was expected due to the pain medication—HYDROMORPHONE—that the child was receiving. Despite ongoing, repeated concerns expressed by the parents, the nurses failed to recognize that the child was not simply sleeping soundly but exhibiting signs of severe, life-threatening hyponatremia.

When the child began experiencing seizure-like activity in the early afternoon, nurses attributed the movements to the child being "fidgety" from pain. The child also began vomiting. Unfortunately, the physician was not kept informed regarding the child's change in cognition, continued oliguria, vomiting, and seizure-like activity. When the critical care intensivist visited the child in the early evening for a routine assessment, he quickly recognized the problem. By then the child exhibited no reflexes or response to painful stimuli. Despite intubation and ventilation support and aggressive treatment of hyponatremia and cerebral edema, the child died the following day.

Although many of the contributing factors and deeply seated root causes of these events differ, 2 common causes are clear. First, lack of professional staff knowledge regarding the causes and signs of hyponatremia, and second, the fail-

ure of professional staff to respond to concerns expressed by several nurses in Case 1, and by the parents in Case 2, regarding the rapidly deteriorating condition of these children.

Hyponatremia and Water Intoxication

Hyponatremia is the most common electrolyte disorder,¹⁵ particularly among hospitalized patients. Studies suggest that more than 4% of postoperative patients develop clinically significant hyponatremia within 1 week of surgery, as do 30% of patients treated in intensive care units (ICUs).¹⁵⁻¹⁸ In general, the causes of hyponatremia are varied, ranging from certain medications (eg, diuretics, heparin, opiates, desmopressin, proton pump inhibitors) and disease states (eg, renal and liver impairment, hypothyroidism or cortisol deficiency) to outpatient environmental conditions (eg, prolonged exercise in a hot environment) and self-imposed conditions (eg, psychogenic polydipsia, feeding infants tap water or formula that is too dilute). However, the causes of hospital-acquired hyponatremia most relevant to the previously described events are twofold: administration of plain D5W or hypotonic saline parenteral solutions postoperatively, and failure to recognize the compromised ability of children to maintain water balance.¹⁵

Review of the literature suggests that administration of hypotonic saline or parenteral fluids without saline is physiologically unsound and potentially dangerous for hospitalized children.¹ A 2003 analysis¹ found more than 50 reported cases of neurologic morbidity and mortality, including 26 deaths, during a 10-year period resulting from hospital-acquired hyponatremia in children who were

receiving hypotonic saline parenteral fluids.¹⁻¹⁴ More than half of these cases occurred in the postoperative setting in previously healthy children who underwent minor surgeries. Children are particularly vulnerable to water intoxication because they are prone to developing a syndrome of inappropriate secretion of antidiuretic hormone (SIADH).¹ Common childhood conditions requiring IV fluids, such as pulmonary and central nervous system infections, dehydration, and the postoperative state, are associated with a nonosmotic—and therefore inappropriate—stimulus for antidiuretic hormone (ADH) production.^{1,14} The postoperative nonosmotic stimulus for ADH release typically resolves by the third postoperative day but can last until the fifth postoperative day.^{1,18} Pain, nausea, stress, opiates, inhaled anesthetics, and the administration of hypotonic saline or solutions without saline also stimulate the excessive release of ADH in children.^{1,14}

Children are also more vulnerable to the effects of cerebral swelling due to hyponatremia because they develop encephalopathy at less significant decreases in normal serum sodium levels than adults and have a poor prognosis if timely therapy is not instituted. In children, there is little room for brain expansion due to a higher brain-to-skull size ratio.^{1,17,19} Children achieve adult brain size by 6 years of age, whereas full skull size is not achieved until 16 years of age.

Hyponatremic encephalopathy can be difficult to recognize in children because the symptoms may be variable.^{2,18} The most consistent symptoms include headache, nausea, vomiting, weakness, mental confusion, and lethargy. Advanced symptoms are signs of cerebral herniation, including seizures, respiratory arrest,

noncardiogenic pulmonary edema, dilated pupils, and decorticate or decerebrate posturing.¹

Irreparable harm can happen when low serum sodium levels are corrected too quickly or too slowly. Once the source of free water has been eliminated, the sodium level is typically increased by 4 to 6 mEq over the first 1 to 2 hours using an isotonic or near isotonic sodium chloride infusate.¹⁵ Patients with seizures, severe confusion, coma, or signs of brainstem herniation may need hypertonic (3%) saline to correct sodium levels, but only enough to arrest the progression of symptoms. Formulas exist for determining the dose of hypertonic saline during replacement therapy.¹⁴ Some clinicians believe that, in serious cases, treatment of hyponatremia should be rapid because the risk of treating too slowly—cerebral herniation—is felt to be greater than the risk of treating too quickly—osmotic demyelination syndrome, which has been associated with lesions in the white matter of the brainstem.¹⁴ These lesions are more common in adults. (Please note: The preceding information is in no way sufficient to guide the treatment of hyponatremia or suggested as an evidence-based standard of care. It was provided only to convey that expert opinions vary regarding prevention and treatment of hyponatremia and to encourage discussion among an interdisciplinary clinical team charged with developing electrolyte replacement protocols.)

Conclusion

Standards of practice should be established for postoperative IV solutions used to hydrate patients—particularly children. The standards should acknowledge that the administration of solutions with saline in maintenance par-

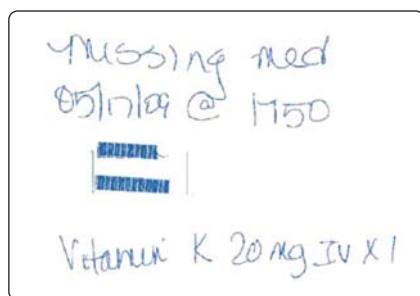


Figure 1. Nurse's interpretation of the vitamin K1 order.

enteral fluids is an important prophylactic measure that can be taken to prevent hyponatremia in children, who are prone to an increase in ADH production.¹⁵ If appropriate, criteria should include when lab studies need to be drawn to determine electrolyte levels in patients receiving IV fluids for hydration over an extended period of time.

Protocols should be established to identify, treat, and monitor patients with hyponatremia, water intoxication, and/or SIADH. Clinically significant hyponatremia may be nonspecific in its presentation; therefore, professional staff must include this in the differential diagnoses in patients presenting with early symptoms or an altered level of consciousness. All physicians, pharmacists, and nurses need a thorough understanding of fluid and electrolyte balance and the pathophysiology of hyponatremia, water intoxication, and SIADH to increase their index of suspicion when symptoms appear, and they need to become more responsive to voiced concerns regarding the patient's condition.

All hospitals should also consider establishing a rapid-response team (RRT) that allows any health care worker to summon an interdisciplinary team to a patient's bedside for a full evaluation when they fear something is seriously wrong with the patient and have expressed

their concerns without an adequate response. The RRT provides an opportunity to step in before a tragedy occurs. Once the RRT has been formed and is functioning well, consider inviting patients and families to call the RRT to address unresolved concerns about their safety and health; subtle changes may be more readily identified as abnormal by family members than by health care providers.

INVESTIGATE AND CLARIFY REQUESTS FOR MISSING DOSES

A pharmacist received a faxed "missing medication" request from a nursing unit for 20 mg of vitamin K1 (phytonadione) IV (see Figure 1) for a patient with an elevated international normalized ratio (INR) of 3.8. The patient, who was being treated for deep vein thrombosis and a pulmonary embolism, had been started on heparin and was recently transitioned to warfarin. The physician determined that an INR of 3.8 was too high and ordered an IV dose of vitamin K1 (see Figure 2) to be given. Although injectable vitamin K1 was in an automated dispensing cabinet (ADC), it could not be removed until a pharmacist verified the order. When the drug failed to become available in the ADC within the usual time it took a pharmacist to review the order, the nurse sent the message about the missing medication in case the pharmacy had overlooked this specific order.

Before dispensing the drug, the pharmacist decided to check the dose with the physician because she read the prescribed dose as 2 mg and the nurse had requested 20 mg. When questioned, the physician responded that he had prescribed 2 mg. The pharmacist had recognized that the dose of

vitamin K1 was considerably higher than it should be for an INR of 3.8. Although the nurse told the pharmacist that the physician was on the unit and wanted the dose given immediately, had the pharmacist not insisted on verifying the dose, the patient could have experienced an adverse outcome. At best, if a 20 mg dose of vitamin K1 IV had been administered, the patient could have been at risk for attenuating the effect of warfarin for weeks; at worst, the patient could have experienced a fatal allergic reaction.¹²

Health care providers have a responsibility to question therapy that does not agree with their knowledge or experience. Even though there may be a rational explanation for a variation from established treatment, it is better to question the variation and learn something new than to acquiesce and dispense or administer what might be a harmful dose. It is also reasonable to expect nurses who administer anticoagulants to be familiar with the typical doses of antagonists. Such information should be included in nursing orientation and annual competency evaluations. Additionally, nurses should have easy access to drug references or anticoagulation protocols to verify prescribed doses of antagonists before administration.

PROVERA, PROZAC, OR PROSCAR?

An order was written for *Provera* (medroxyPROGESTERone)

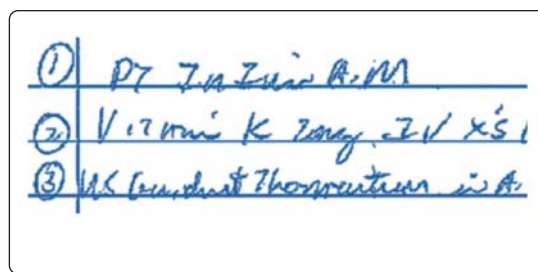


Figure 2. How much vitamin K1 was prescribed?

A photograph of a handwritten prescription on lined paper. The text is written in cursive and reads "Provera 10 mg po daily". The word "Provera" is written in a larger, more prominent script than the rest of the prescription.

Figure 3. Order for *Provera* misread as *Prozac*.

mg orally (PO) daily (see Figure 3). During order entry, the pharmacist misinterpreted the order as *Prozac* (fluoxetine) 10 mg PO daily. The nurse did not detect the error when verifying the order in the eMAR. The patient received 1 dose of *Prozac*. The physician discovered the error the next day while he was reviewing the patient's medication list (which is a highly recommended form of redundancy that has detected many errors). The handwritten order was shown to several nurses, pharmacists, and physicians. Most read the order as *Provera* but one physician thought it was *Prozac*. One nurse guessed it was *Provera* but also said it could be *Proscar* (finasteride). Poor handwriting was a contributing factor, as was the fact that *Provera* is infrequently prescribed whereas *Prozac* is a commonly prescribed drug, perhaps biasing the reader's interpretation as "*Prozac*" on the handwritten prescription.

REFERENCES

1. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics*. 2003;111(2):227-230.
2. Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. *BMJ*. 1992;304(6836):1218-1222.
3. Burrows FA, Shutack JG, Crone RK. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric pop-

ulation. *Crit Care Med*. 1983;11(7):527-531.

4. Lieh-Lai MW, Stanitski DF, Sarnaik AP, et al. Syndrome of inappropriate antidiuretic hormone secretion in children following spinal fusion. *Crit Care Med*. 1999;27(3):622-627.

5. Chen MK, Schropp KP, Lobe TE. Complications of minimal-access surgery in children. *J Pediatr Surg*. 1996;31(8):1161-1165.

6. Armour A. Dilutional hyponatraemia: a cause of massive fatal intraoperative cerebral edema in a child undergoing renal transplantation. *J Clin Pathol*. 1997;50(5):444-446.

7. Levine JP, Stelnicki E, Weiner HL, et al. Hyponatremia in the postoperative craniofacial pediatric patient population: a connection to cerebral salt wasting syndrome and management of the disorder. *Plast Reconstr Surg*. 2001;108(6):1501-1508.

8. Eldredge EA, Rockoff MA, Medlock MD, Scott RM, Millis MB. Postoperative cerebral edema occurring in children with slit ventricles. *Pediatrics*. 1997;99(4):625-630.

9. Hughes PD, McNicol D, Mutton PM, Flynn GJ, Tuck R, Yorke P. Postoperative hyponatraemic encephalopathy: water intoxication. *Aust N Z J Surg*. 1998;68(2):165-168.

10. McRae RG, Weissburg AJ, Chang KW. Iatrogenic hyponatremia: cause of death following pediatric tonsillectomy. *Int J Pediatr Otorhinolaryngol*. 1994;30(3):227-232.

11. Judd BA, Haycock GB, Dalton RN, et al. Antidiuretic hormone following surgery in children. *Acta Paediatr Scand*. 1990;79:461-466.

12. Soroker D, Ezri T, Lurie S, et al. Symptomatic hyponatraemia due to inappropriate antidiuretic hormone secretion following minor surgery. *Can J Anaesth*. 1991;38(2):225-226.

13. Paut O, Rémond C, Lagier P, Camboulives J. Severe hyponatremic encephalopathy after pediatric surgery: report of seven cases and recommendations for management and prevention [in

French]. *Ann Fr Anesth Reanim*. 2000;19(6):467-473

14. Agut Fuster MA, del Campo Biosca J, Rodriguez AF, et al. Post-tonsillectomy hyponatremia: a possible lethal complication [in Spanish]. *Acta Otorrinolaringol Esp*. 2006;57(5):247-250.

15. Craig S. *eMedicine Emergency Medicine: Hyponatremia*. WebMD Web site. <http://emedicine.medscape.com/article/767624-overview>. Accessed September 4, 2008. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. 2006;119(7)(suppl 1):S30-S35.

16. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*. 2003;337(1-2):169-172.

17. Hoorn E, Lindemans J, Zietse R. Hyponatremia in hospitalized patients: epidemiology, etiology and symptomatology. *J Am Soc Nephrol*. 2004;15:561(A).

18. Brown RG. Disorders of water and sodium balance. *Postgrad Med*. 1993;93(4):227-228, 231-234, 239-240.

19. Watanabe N, Tani M, Tanaka Y, et al. Severe hyponatremia with consciousness disturbance caused by hydroxyurea in a patient with chronic myeloid leukemia [in Japanese]. *Rinsho Ketsueki*. 2004;45(3):243-246.

20. Yeates KE, Singer M, Ross Morton A. Salt and water: a simple approach to hyponatremia [published correction appears in *CMAJ*. 2004;170(6):93]. *CMAJ*. 2004;170(3):365-369.

21. Fugate SE, Nichols SM, Cudd LA. Impaired warfarin response secondary to high-dose vitamin K1 for rapid anticoagulation reversal. *Pharmacotherapy*. 2004;24(9):1213-20.

22. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K1 antagonists: American College Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6)(suppl):160-198. ■