The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety.

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Hospital-Acquired Acute Hyponatremia: Two Reports of Pediatric Deaths

Two pediatric deaths due to acute hyponatremia associated with intravenous (IV) administration of hypotonic solutions, one in a postsurgical setting and the other in a medical setting, have been voluntarily reported to ISMP Canada. Acute hyponatremia is defined as a decline in serum sodium within a 48-hour period to less than 130 mmol/L. This abrupt change can lead to cerebral edema as a result of electrolyte-free water moving into the brain cells. Acute hyponatremia can be fatal for both children and adults; however, children are more vulnerable to the effects of fluid and electrolyte imbalance. The early signs of acute hyponatremia and rising intracranial pressure are often nonspecific and include nausea, vomiting, headache, and decreasing level of consciousness. Information from the 2 voluntary incident reports is shared here to enhance healthcare practitioners' understanding of the potential for fatal hyponatremia in children.

Incident Reports

Case 1

A 4-year-old child who weighed about 15 kg underwent tonsillectomy as day surgery. No abnormalities were noted during a preadmission assessment the day before the surgery. The tonsillectomy was performed under general anesthesia; a breathing tube was inserted and the child was mechanically ventilated during the procedure. According to the records from the operating room, the child received a total of 250 mL normal saline IV (0.9% sodium chloride). After the procedure, an infusion of 3.3% dextrose and 0.3% sodium chloride solution (referred to herein as "2/3 and 1/3")* was ordered for IV administration at 55 mL per hour. Oral intake of fluids was also encouraged. The child was transferred to a patient care area with orders to be discharged home when drinking well.

Shortly after arriving in the patient care area, the child experienced several episodes of vomiting. Oral intake of clear fluids over the next several hours was about 200 mL. The child was kept in hospital, and the IV administration of "2/3 and 1/3" was continued as originally ordered over the rest of the day and night. The child voided several times, but the amount was unknown. Overnight, the child became incontinent and was noted to be drowsy. Towards the morning, the child had several seizures, which were treated initially with lorazepam and later with phenobarbital. Blood testing indicated a sodium level below 120 mmol/L. The IV solution was changed to sodium chloride 3%, and the child was transferred to a regional pediatric centre. The child died shortly thereafter. The cause of death was severe cerebral edema with brain herniation due to acute hyponatremia.

Case 2

A previously healthy 3-year-old child was brought to an emergency department with a one-day history of vomiting and diarrhea. The child's pulse was more than 125 beats per minute, and the blood pressure was 85/60 mm Hg. The child's mucosal membranes were dry and the eyes sunken. Laboratory testing indicated normal serum electrolytes, elevated blood urea nitrogen (BUN), and normal creatinine; a urine test was positive for ketones. In the emergency department, the child received 2 boluses of normal saline by IV administration, totalling about 450 mL. Follow-up blood work revealed that the sodium level was 138 mmol/L and BUN had decreased to within normal limits. The child was admitted, and "2/3 and 1/3" was administered at 130 mL per hour IV. Over the course of the next 12 hours (through the evening and overnight), the child voided about 110 mL urine in total and received over 1.5 litres of "2/3 and 1/3". The child's nausea continued.

The next day, the child voided once, but the amount was not determined or recorded. Shortly thereafter, the child experienced incontinence of urine and seemed to be sleepy. A few hours later, the child appeared lethargic and rigid. The infusion was stopped, and blood tests revealed a sodium level below 120 mmol/L and lower-than-normal levels of potassium, BUN, and creatinine. The child experienced a seizure and was treated with lorazepam. Hypertonic saline was ordered, but none was available, so mannitol was administered IV, followed by

* **The combination of 3.3% dextrose and 0.3% sodium chloride (known as 2/3 and 1/3) contains only 51 mmol/L of sodium. Outside of the body, the osmolarity of the solution is 269 mOsmol/L (sodium and dextrose combined). Once the solution is infused, however, the dextrose is rapidly metabolized, which leaves two-thirds of the solution (667 mL) as electrolyte-free water and renders the solution *extremely hypotonic*.**

a bolus of normal saline. Because of continued seizure activity and oxygen desaturation, the child was intubated and ventilated. Shortly thereafter, the child experienced cardiac arrest and could not be resuscitated. The cause of death was cerebral edema with brain herniation due to acute hyponatremia.

Background Information about Acute Hyponatremia

Hyponatremia can occur if there is a disproportionate loss of sodium such as occurs with primary kidney disease or conditions that affect the ability of the kidneys to conserve sodium. It can also occur because of a disproportionate gain of electrolyte-free water in the vascular compartment, also known as dilutional hyponatremia or water intoxication. The increased ratio of free water to sodium in the vascular space will cause the water to move from this extracellular compartment into the intracellular compartment until osmolality is equalized—free water will enter body cells (i.e., brain cells) and cellular edema will result.

In acute hyponatremia, the brain cells are unable to compensate for the rapid decrease in serum osmolality; as such, minor increases in electrolyte-free water can lead to disproportionately large increases in intracranial pressure due to swelling of the brain cells.[1,2,3] Children exhibit symptoms more quickly than adults in response to abnormal sodium levels because there is less room for the brain cells to swell (the brain reaches its adult size by the time the child is 6 years old, but the skull does not reach adult size until a person is 16 years of age).[3]

Since the early signs and symptoms of acute hyponatremia are often nonspecific, healthcare professionals may attribute them to other causes, such as the postoperative effects of anesthetics, medications administered for pain, or the presenting illness. A rapid decline in serum levels of sodium leading to symptoms of increased intracranial pressure is a medical emergency, as further increases in brain-cell swelling can cause seizures, respiratory depression, coma, irreversible brain damage, or brain herniation and death.

The kidney is the main regulator of water through the activity of antidiuretic hormone (ADH). ADH (also known as vasopressin) acts directly on the kidneys, causing them to reabsorb water, which helps to maintain the serum sodium, and thus the osmolality of the blood, within normal limits. A reduction in serum osmolality (as occurs with a reduction in serum sodium) typically inhibits the release of ADH, whereas an increase in serum osmolality causes the release of ADH. This "osmotic" feedback system in the body allows for variability in electrolyte-free water intake so that serum osmolality and serum sodium remain within normal range.

ADH is also known to be released in response to numerous "nonosmotic" stimuli, even when serum sodium falls to below-normal values. One of the most potent stimuli for ADH release is nausea and vomiting. Other nonosmotic stimuli for the release of ADH include pain, stress, gastroenteritis, hypoxia, positive pressure ventilation, trauma, and commonly used medications such as opioids.[1,2,4] Numerous disease states such as pneumonia are also known to cause the release of ADH. The release of ADH after surgery in response to nonosmotic stimuli typically resolves by the third postoperative day but can last up to the fifth postoperative day.[2] Children appear to be at particular risk after surgical procedures, and deaths have been reported after even minor surgery.[3,5,6]

Importantly, *in the presence of ADH, the kidneys cannot eliminate excess electrolyte-free water.*[1,2] In addition to the administration of hypotonic parenteral solutions such as "2/3 and 1/3", oral and enteral intake may be a source of electrolyte-free water that contributes to the development of acute hyponatremia (e.g., hypotonic feeds, water, ice chips).[7] Experts have noted that hyponatremia is the most common electrolyte disturbance among children being treated in hospital because such patients are commonly exposed to nonosmotic stimuli for ADH and also because the administration of hypotonic solutions is routine practice in many hospitals.[1,2]

Discussion

Incidents of hospital-acquired acute hyponatremia in children leading to severe harm and death have been reported internationally. Various literature reports,[1-3,5,6,8] pediatric inquests,[9] and a recent newsletter from the US Institute for Safe Medication Practices[10] have highlighted awareness of cases of acute hyponatremia leading to the in-hospital deaths of children who were otherwise healthy. The National Patient Safety Agency in the United Kingdom has identified hospital-acquired hyponatremia in children as a major patient safety issue. Safety alerts and guidelines for the administration of fluids to children have been published as a result.[11-14] In Canada, the Canadian Medical Protective Association recently highlighted a case of hospital-acquired hyponatremia in a child.[15] A provincial coroner identified 6 pediatric deaths related to acute hyponatremia in hospital settings over a 10-year period and provided a guideline for practitioners administering parenteral fluids to children.[16]

There appears to be general consensus that isotonic fluids such as normal saline should be used for children during surgery, and in the treatment of moderate to severe hypovolemia; however, there is debate as to which solution is the best choice for maintenance of hydration.[1-6,8,17-28] Pediatric experts are questioning the widespread use of hypotonic solutions for parenteral maintenance, a practice based on a formula that was developed more than 50 years ago.[29] The formula is derived from minimum free-water requirements based on caloric expenditure per kilogram of body weight. Experts argue that this formula overestimates maintenance requirements for a variety of reasons; most importantly, the formula presumes normal excretion of free water by the kidneys and thus does not take into account ADH released in response to nonosmotic stimuli, a process that was identified since the original development of the formula and that is commonly seen in hospitalized children. In one recent study, a key factor in the development of hospital-acquired hyponatremia was the use of hypotonic maintenance solutions.[30] A variety of studies, including randomized trials, are answering questions about the use of maintenance fluids for children.[30-32] Experts do agree, however, that there is no single IV solution that is ideal for all children.

Parenteral fluids administered for the purpose of hydration have not traditionally been viewed with the same rigour as medications. These fluids are usually distributed through a central supply and redistribution service or through hospital stores as part of the materials management division of hospital operations. Many Canadian pediatric centres have recognized hospital-acquired hyponatremia as an important issue that merits attention and have revised, or are in the process of revising, their practice guidelines and management of fluids and electrolytes accordingly.[33-35]

Recommendations and Considerations

Ensure that guidelines for fluid and electrolyte therapy are aligned with the regional pediatric referral centre within the province or territory and that these guidelines include:

- the optimal choices for parenteral solutions and rates of administration;
- the circumstances under which hypotonic solutions may be used;
- the minimum requirements and frequency for:
  - monitoring serum electrolytes,
  - accurate measurement of all sources of intake and output (during every shift, and with an ongoing cumulative balance);
- early involvement of the most responsible physician in cases where fluid intake greatly exceeds urine output;
- how to identify, treat, and monitor patients with electrolyte disorders such as hyponatremia (e.g., specify when additional monitoring such as measurement of urine osmolarity and urine electrolytes are required);
- criteria for expert consultation.

Engage family members whenever they express concerns about their child's behaviour—subtle changes may be more readily identified as abnormal by family members than by healthcare providers and thus can provide an invaluable source of assessment information.

It is hoped that this bulletin will serve as an alert to all healthcare practitioners, particularly those providing care to children.

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