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Prevention of Hospital-Acquired Hyponatremia: A Case for Using Isotonic Saline

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ABSTRACT. *Objective.* The current standard of care in pediatrics is to administer hypotonic saline in maintenance parenteral fluids. The safety of this approach has never been evaluated.

Methods. A review of the literature reveals that the administration of hypotonic fluids is potentially dangerous and may not be physiologic for the hospitalized child.

Results. There have been >50 reported cases of neurologic morbidity and mortality, including 26 deaths, in the past 10 years resulting from hospital-acquired hyponatremia in children who were receiving hypotonic parenteral fluids. Common childhood conditions requiring parenteral fluids, such as pulmonary and central nervous system infections, dehydration, and the postoperative state, are associated with a nonosmotic stimulus for antidiuretic hormone production, which can lead to free water retention and hyponatremia. Children are at particularly high risk of developing symptomatic hyponatremia as they have a larger brain-to-skull size ratio.

Conclusions. The administration of isotonic saline in maintenance parenteral fluids is the most important prophylactic measure that can be taken to prevent the development of hyponatremia in children who receive parenteral fluids. *Pediatrics* 2003;111:227–230; *hyponatremia, [illegible], treatment, fluid, intravenous, encephalopathy.*

ABBREVIATIONS. ADH, antidiuretic hormone; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

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The basic principles for prescribing maintenance parenteral fluids in children were laid down in the 1940s and 1950s and culminated with Holliday and Segar's landmark paper in 1957[1] describing a simple formula for determining the maintenance need for water in children and recommending the use of a hypotonic saline solution, equivalent to 0.2% sodium chloride in 5% dextrose in water. Since that time, recommendations for prescribing maintenance parenteral fluid therapy have remained unchanged.[2] Although Holliday and Segar's formula for determining water needs clearly has passed the test of time, their recommendations for prescribing hypotonic saline need to be reassessed. Increasing evidence has shown that hypotonic maintenance fluids can lead to potentially fatal hyponatremia in cases of excess antidiuretic hormone (ADH) production.[3–6] Although it is well-established that isotonic saline should be used for fluid resuscitation in children to raise circulatory volume while preventing the development of hyponatremia,[7] it has not been an accepted practice to use isotonic saline as a maintenance fluid. We review the evidence supporting our view that isotonic saline should be used in favor of hypotonic saline in maintenance fluids in hospitalized children, who are prone to have an increase in ADH production, as this is least likely to result in hyponatremia.

WHY HYPOTONIC MAINTENANCE PARENTERAL FLUIDS ARE CURRENTLY USED

Maintenance needs for water in children have been shown to parallel energy metabolism.[8–10] Maintenance requirements for electrolytes are less clear. Holliday and Segar[1] conceded this point, writing, "With respect to maintenance needs for electrolytes, less precise data are available and figures considerably in excess of minimum requirements are readily handled." In 1953, Talbot et al[11] recognized the potential danger of administering hypotonic fluid in states of ADH excess, stating that the "administra-

tion of dextrose in water solution at a rate of more than approximately 1100 mL/M²/24 hrs may induce water intoxication" and that the "risk of water intoxication may be reduced to small proportions by the administration of 100 or more mosm of organic solute to each liter of solution." The safety of administering maintenance hypotonic parenteral fluids has never been evaluated prospectively, and Holliday and Segar noted that approximately one third of children and adults receiving parenteral therapy had urinary concentration outside of a desirable range.

The primary basis for the current recommendation of prescribing 3.0 and 2.0 mEq/100 kcal/24 h sodium and potassium, respectively, in maintenance fluids is that this roughly reflects the electrolyte composition of breast and cow milk.[1,8–10] This electrolyte composition will also result in a urine osmolality of approximately 400 mOsm/kg/H_2O, which was believed to be ideal, as it is between the range of urinary concentrating capacity.[11] Although it has been well-established that isotonic saline could be tolerated without any adverse effects, the use of isotonic saline has been avoided to prevent excess urinary water losses in conditions with impaired renal concentrating ability and to prevent the development of postoperative edema.[9–11] Whereas these recommendations may be appropriate for the healthy child, they may not apply to ill children, who are much more likely to have a nonosmotic stimulus for ADH production (Table 1). At the time that these recommendations were made, it was not yet fully appreciated that many conditions could lead to impaired free water excretion as a result of ADH excess. It is our intent to alert physicians to the potential dangers of using hypotonic maintenance fluids in children who may have an impaired ability to excrete free water, as this can lead to clinically significant hyponatremia.

HOSPITAL-ACQUIRED HYPONATREMIA

In 1957, the same year that Holliday and Segar published their paper on maintenance water needs, Schwartz et al[12] described the first case of "the syndrome of inappropriate secretion of antidiuretic hormone" (SIADH).[13] SIADH is a disorder that can lead to hyponatremia as a result of the nonphysiologic secretion of ADH, which leads to free water retention followed by a natriuresis that maintains fluid balance at the expense of serum osmolality. SIADH is 1 of the most common causes of hyponatremia in both children and adults in a hospital setting.[14] It has been reported in numerous conditions but primarily affects children with central nervous system and pulmonary disorders and as a side effect of medications. Many common childhood conditions that require parenteral fluids cause SIADH, such as pneumonia,[15] bronchiolitis,[16] asthma,[17] positive pressure ventilation, CNS infections,[18] and head trauma.[19] Other stimuli for ADH release that can lead to hyponatremia in children are emesis, pain, stress, and hypoxia.[20] There are many clinical settings where children are at risk for developing hyponatremia as a result of nonosmotic stimuli for ADH release (Table 1).

A common reason that hospitalized children receive parenteral fluids is to treat isotonic dehydration. Although isotonic saline is recommended for acute volume expansion, hypotonic fluids with 0.45% sodium chloride are currently recommended for the remainder of the deficit therapy.[21] Volume depletion is a potent stimulus for ADH production. The administration of hypotonic fluids to children with dehydration can result in acute hyponatremia secondary to free water retention.[22] Hypotonic fluids are even recommended as parenteral fluid therapy in children with meningitis.[23] Such children frequently have dehydration in addition to other nonosmotic stimuli for ADH production, and the administration of hypotonic fluids can lead to worsening neurologic deterioration secondary to the development of hyponatremia.

Postoperative children are at especially high risk for developing hyponatremia, and there have been many associated fatalities.[3,17,24–30] Contributing factors to hyponatremia in the postoperative setting comprise a combination of nonosmotic stimuli for ADH release, such as subclinical volume depletion, pain, nausea, stress, edema-forming conditions, and the administration of hypotonic fluids. The postoperative nonosmotic stimuli for ADH release typically resolve by the third postoperative day but can last until the fifth postoperative day.[17] The most important factors that lead to postoperative hyponatremia are the failure to recognize the compromised ability of the patient to maintain water balance and the administration of hypotonic fluids.

There have been >50 reported cases of neurologic morbidity and mortality, including 26 deaths, resulting from hospital-acquired hyponatremia in children who were receiving hypotonic fluids.[3–5,15,26–29,31–3] More than half of these cases occurred in the post

TABLE 1. Clinical Settings of Increased ADH Release in Children

Hemodynamic Stimuli for ADH Release (Decreased Effective Circulation Volume)	Nonhemodynamic Stimuli for ADH Release
Hypovolemia	Central nervous system disturbances
Nephrosis	Meningitis, encephalitis, brain tumors, head injury
Cirrhosis	Pulmonary disease
Congestive heart failure	Pneumonia, asthma, bronchiolitis
Hypoaldosteronism	Cancer
Hypotension	Medications
Hypoalbuminemia	Cytoxan, Vincristine, Morphine
	Nausea, emesis, pain, stress
	Postoperative state

TABLE 2. Electrolyte-Free Water in Parenteral Fluids

Intravenous Fluid	Sodium (mEq/L)	Osmolality (mOsm/kg/H_2O)	% Electrolyte-Free Water*
5% Dextrose in water	0	252	100
0.2% Sodium chloride in 5% dextrose in water	34	321	78
0.45% Sodium chloride in 5% dextrose in water	77	406	50
Lactated Ringer's	130	273	16
5% Dextrose Lactated Ringer's	130	525	16
0.9% Sodium chloride in 5% dextrose in water	154	560	0

* Based on a sodium plus potassium concentration in the aqueous phase of plasma of 154 mEq/L, assuming that plasma is 93% water with a serum sodium of 140 mEq/L and a potassium concentration of 4 mEq/L.

operative setting in previously healthy children who underwent minor surgery. Arieff et al[3] reported on 16 previously healthy children who died or experienced permanent neurologic damage as a result of hyponatremic encephalopathy soon after receiving hypotonic fluids after minor surgical procedures or for the treatment of common childhood infections. McJunkin et al[5] and Moritz and Ayus[6] noted that the major factor that results in neurologic deterioration in children with La Crosse encephalitis was mild hyponatremia developing after the administration of hypotonic fluid. Halberthal et al[4] reported on 23 children, without an underlying disease that impaired water handling, who developed acute symptomatic hyponatremia after the administration of hypotonic fluids. Hyponatremia in these cases seemed to be attributable to a combination of hypotonic fluid administration and ADH excess. The above authors and others[30,35] have cautioned against the routine use of hypotonic maintenance fluids in children.

Children are at particularly high risk for developing symptomatic hyponatremia as they develop hyponatremic encephalopathy at higher serum sodium concentrations than adults and have a poor prognosis if timely therapy is not instituted. This seems to be attributable to the higher brain-to-skull size ratio in children, which leaves less room for brain expansion.[3,36] Children achieve adult brain size by 6 years of age, whereas full skull size is not achieved until 16 years of age. Female adolescents may also be at increased risk of developing hyponatremic encephalopathy, as women of reproductive age are >30 times more likely to develop hyponatremic encephalopathy than are men, as a result of diminished ability to adapt to hyponatremia by decreasing brain volume.[36,37]

Hyponatremic encephalopathy can be difficult to recognize in children, as the symptoms can be variable and do not correlate with either the serum sodium concentration or the rapidity of development of hyponatremia.[3] The most consistent symptoms of hyponatremia are headache, nausea, vomiting, emesis, and weakness. Advanced symptoms are signs of cerebral herniation, with seizures, respiratory arrest, noncardiogenic pulmonary edema,[38,39] dilated pupils, and decorticate posturing.[3] Failure to recognize hyponatremic encephalopathy and initiate appropriate therapy will result in a poor neurologic outcome.[3,29]

WHY ISOTONIC MAINTENANCE PARENTERAL FLUIDS SHOULD BE USED

The administration of isotonic maintenance fluids is the most important prophylactic measure that can be taken to prevent the development of hyponatremia in children who are receiving parenteral fluids. Commonly used intravenous fluids have a significant amount of free water that can contribute to hyponatremia (Table 2); therefore, they should be used with caution in maintenance fluids, to mix intravenous medications or to keep a vein open. Even isotonic saline can lead to hyponatremia if excessive fluid is administered in the presence of a fixed urine osmolality with impaired urinary dilution.[40] If an isotonic solution of 300 mOsm/kg/H_2O is administered in a state of excess vasopressin, such as SIADH or the postoperative state, for which the urine osmolality may be fixed at 500 mOsm/kg/H_2O, then a natriuresis that will result in the generation and retention of free water and the development of hyponatremia will ensue. An isotonic solution will have approximately 154 mEq/L monovalent cations, sodium plus potassium, as the average concentration of sodium plus potassium in the aqueous phase of plasma is 154 mEq/L. Although no 1 fluid rate or composition will be appropriate for all children, isotonic saline in 5% dextrose in water seems to be the safest fluid composition in most hospitalized patients. If potassium chloride is to be added to the parenteral fluids, then the sodium concentration can be lowered proportionally to maintain isotonicity. Lactated ringers with 20 mEq/L potassium chloride in 5% dextrose in water would also be an isotonic fluid. Physicians must assess children carefully to choose the most appropriate parenteral fluid rate and composition before initiating therapy. The maintenance fluid requirements of the term and preterm neonate may differ from the older child as a result of unique physiologic issues, and our recommendations do not extend to this group of patients. Children with ongoing free water losses or a free water deficit will require a more hypotonic fluid. In children with illnesses that can lead to fluid overload, such as nephrosis, cirrhosis, congestive heart failure, and glomerulonephritis, both sodium and fluid restriction is of paramount importance to avoid worsening fluid overload and the development of hyponatremia. Hospitalized children who are receiving parenteral fluid therapy should be considered at risk for developing hyponatremia and monitored closely

through daily weights, fluid balance, blood pressure, observing for signs of edema, and monitoring the serum sodium concentration. Isotonic saline seems to be the preferred fluid for administration to hospitalized patients, as they are at high risk for developing hyponatremia as a result of factors that lead to ADH excess.

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"Human progress can be compared to a storm-lashed sea; men must commit a thousand errors to arrive at the truth."

—Arj Turgot (1751)