Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study
Ewout J. Hoorn, Denis Geary, Maryanne Robb, Mitchell L. Halperin and Desmond Bohn
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ABSTRACT. Objective. To develop hyponatremia (plasma sodium concentration \( [P_{Na}] < 136 \) mmol/L), one needs a source of water input and antidiuretic hormone secretion release to diminish its excretion. The administration of hypotonic maintenance fluids is common practice in hospitalized children. The objective of this study was to identify risk factors for the development of hospital-acquired, acute hyponatremia in a tertiary care hospital using a retrospective analysis.

Methods. All children who presented to the emergency department in a 3-month period and had at least 1 \( P_{Na} \) measured (\( n = 1586 \)) were evaluated. Those who were admitted were followed for the next 48 hours to identify patients with hospital-acquired hyponatremia. An age- and gender-matched case-control (1:3) analysis with patients who did not become hyponatremic was performed.

Results. Hyponatremia \( (P_{Na} < 136 \) mmol/L) was documented in 131 of 1586 patients with \( \geq 1 \) \( P_{Na} \) measurements. Although 96 patients were hyponatremic on presentation, our study group consisted of 40 patients who developed hyponatremia in hospital. The case-control study showed that the patients in the hospital-acquired hyponatremia group received significantly more EFW and had a higher positive water balance. With respect to outcomes, 2 patients had major neurologic sequelae and 1 died.

Conclusion. The most important factor for hospital-acquired hyponatremia is the administration of hypotonic fluid. We suggest that hypotonic fluid not be given to children when they have a \( P_{Na} \) < 138 mmol/L.

ABBREVIATIONS. ECF, extracellular fluid; ADH, antidiuretic hormone; \( P_{Na} \), plasma sodium concentration; EFW, electrolyte-free water; TBW, total body water.

Hyponatremia is the most frequently encountered electrolyte disorder in hospitalized patients\(^1\)\(^,\)\(^2\) and suggests that there is a surplus of water and/or a deficit of \( Na^+ \) in the extracellular fluid (ECF) compartment. Hence, there must be a source of water and actions of antidiuretic hormone secretion (ADH) to impair its excretion.\(^3\) In children, the source of water is frequently the administration of hypotonic intravenous fluids. When the plasma sodium concentration \( (P_{Na}) \) falls acutely to <130 mmol/L, brain cell swelling may develop and be sufficient to lead to a devastating neurologic outcome. The most frequent clinical setting for acute hyponatremia is after elective surgery.\(^4\)\(^,\)\(^5\)\(^,\)\(^6\) In this situation, the stimuli for the release of ADH are usually nonosmotic (pain, anxiety, nausea, and the use of pharmacologic agents such as narcotics and inhalational anesthetics). The problem is compounded when hypotonic fluids are given while the excretion of hypotonic urine is impaired.\(^7\)

We recently reported on the development of acute hyponatremia in children who received hypotonic intravenous fluids.\(^6\) We identified during a 10-year period 23 patients who had a rapid reduction in \( P_{Na} \) after surgery or in association with the administration of large amounts of hypotonic fluids. There was a 30% adverse outcome rate (death or neurologic injury). However, because that study was based on either a hospital discharge diagnosis of acute hyponatremia or patients who were referred to the critical care unit because of cerebral edema and brainstem herniation, it is unlikely to be an accurate reflection of the numbers at risk for an adverse neurologic event. We therefore conducted the present study to determine the importance of intravenous fluid therapy and the underlying diseases in its development.

METHODS

Approval was obtained from the Institutional Research Ethics Board to conduct a retrospective review of patients who were seen in or admitted through our hospital emergency department.

Study Group

Hyponatremia was defined as a \( P_{Na} < 136 \) mmol/L. During the 3-month period from November 2000 to February 2001, there were 13 506 visits to the emergency department at the Hospital for Sick Children in Toronto. Those who had at least 1 \( P_{Na} \) value <136 mmol/L were identified. We then focused on patients who had a fall in \( P_{Na} \) in hospital—the hospital-acquired hyponatremia group.

The following general clinical data were included in our analysis: age, gender, weight, diagnosis, and medications. We looked for possible central nervous system symptoms of acute hyponatremia (headache, nausea, vomiting, seizures, and changes in sen-
Analysis of the Basis for a Fall in $P_{Na}$

Patients who developed hyponatremia in hospital were analyzed in greater detail because we could evaluate risk factors that contributed to its development. We calculated the amount of electrolyte-free water (EFW) input using the tonicity and volume of the administered fluid. For example, the commonly used solution for maintenance fluids in our institution is 3.3% dextrose in 0.3% NaCl (51 mmol of Na+ per liter), which is one third of the amount present in an isotonic saline. Therefore, two thirds of the volume of this solution can be thought of as EFW. In our calculations, we included potassium (K+) in defining tonicity. These calculations were also performed for oral solutions.

The influence of EFW on the $P_{Na}$ was analyzed using the initial measured $P_{Na}$ and total body water (TBW) estimated as 60% of body weight, except for neonates in whom TBW was calculated as 70% of body weight. If, for example, the $P_{Na}$ fell from 140 to 135 mmol/L as a result of a positive balance for EFW, then the TBW in a 10-kg person would have to increase from 6000 mL to 6220 mL (positive balance of 220 mL of EFW). Included in calculations for output were insensible losses, using an average of 14 mL/kg/day in the absence of fever. Finally, we recorded likely reasons for high ADH levels from data in the history (disease, symptoms, drugs, and surgery) and physical examination (ECF contraction).

We also compared the patients with hospital-acquired hyponatremia with a control group of age, gender, and weight-matched patients who had $\geq 2$ $P_{Na}$ measurements in which the $P_{Na}$ was $>136$ mmol/L using a 1:3 match. Cases with a reason for a shift of water from the intracellular fluid to the ECF compartment (eg, hyperglycemia) or those who were given hypertonic mannitol were excluded from this analysis. We identified all patients who had $\geq 1$ serum electrolyte measurements from the hospital laboratory database.

Analytical Methods and Calculations

A retrospective case-control study was performed using a t test and a $\chi^2$ test. Correction for multiple variable testing included using the Bonferroni correction. In this study confirm that it was not uncommon for hyponatremia to develop in the first 48 hours of admission to hospital, related in large part to intravenous fluid administration. The level of $P_{Na}$ that we used for eligibility criterion is consistent with previously published definitions and was the median level found in a large published series of children who presented to a hospital with acute medical illnesses. Groups of children who previously have been reported to be at risk are those with meningitis, encephalitis, head injury, bronchiolitis, gastroenteritis, and chronic lung disease of prematurity and in association with chemotherapy. This list was not all-inclusive because other nonosmotic stimuli were present in our population with hospital-acquired hyponatremia (Table 1). Hyponatremia is also a common event after elective surgery and when acute (<48 hours) can lead to catastrophic neurologic sequelae. Children above the line of identity), and the other did not receive enough EFW to explain their fall in $P_{Na}$ (points below the line of identity). The source of this EFW load was predominantly the infusion of hypertonic fluids (66%), whereas in the remainder, the fall in $P_{Na}$ could be attributed to the oral intake of EFW; these latter patients could have had an occult source of water intake, a reason to shift EFW out of cells (eg, a catabolic state, the excretion of hypertonic urine). The main reason for this ECF volume expansion may have been the bolus infusion of more isotonic saline than needed to reexpand the ECF volume.

We identified 16 patients with insufficient EFW to cause the observed degree of fall in their $P_{Na}$ (Fig 1); 11 received a bolus of 0.9 NaCl (45 ± 42 mL/kg/h; 15% expansion of ECF if all retained) on the basis of the presumption that they had ECF contraction. None of the patients on or above the line of identity received boluses of fluid.

Case-Control Study

The in-hospital group with a fall in their $P_{Na}$ received 3-fold more EFW and had a greater positive fluid balance than the control group ($P < .001$ and $P = .02$, respectively; Table 1). Although this in-hospital group received less Na+ per kilogram of body weight, this difference was not statistically significant. The amount of fluid infused was not only significantly higher in this in-hospital group but also well above that recommended by the standard formula for maintenance fluid administration and well above what we now calculate for maintenance fluids. Our analysis showed that there were no significant differences related to the underlying disease, that the symptoms of nausea and vomiting were significantly more prevalent in the in-hospital group, and that patients in the in-hospital group underwent surgery more frequently ($P < .05$). Finally, likely reasons for high levels of ADH in patients with hospital-acquired hyponatremia were found to be mainly of nonosmotic origin (symptoms, drugs, and disease; Table 1).

DISCUSSION

The principal results in this study confirm that it was not uncommon for hyponatremia to develop in the first 48 hours of admission to hospital, related in large part to intravenous fluid administration. The level of $P_{Na}$ that we used for eligibility criterion is consistent with previously published definitions and was the median level found in a large published series of children who presented to a hospital with acute medical illnesses. Groups of children who previously have been reported to be at risk are those with meningitis, encephalitis, head injury, bronchiolitis, gastroenteritis, and chronic lung disease of prematurity and in association with chemotherapy. This list was not all-inclusive because other nonosmotic stimuli were present in our population with hospital-acquired hyponatremia (Table 1). Hyponatremia is also a common event after elective surgery and when acute (<48 hours) can lead to catastrophic neurologic sequelae.
with chronic hyponatremia are not at risk for the development of cerebral edema.\textsuperscript{32,33}

There are 2 requirements for a fall in $P_{Na}$: the presence of ADH and a source of water input. Although it should not be surprising to find elevated ADH levels in acutely ill patients,\textsuperscript{18} this will not cause hyponatremia in the absence of water input. The major source for water input in our study was the infusion of a large amount of hypotonic fluid. Because close to half of the cases received a higher

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**Fig 1.** The relationship between EFW administration and the fall in $P_{Na}$. *Overlap of 2 points. Points represent individual patients with hospital-acquired hyponatremia ($n = 37$). The case numbers next to the dots refer to patients whose urine output is known and correspond with those in Fig 2. The solid line represents the amount of EFW that would need to be retained to cause the observed fall in $P_{Na}$. The patients whose points fell on or above the line of identity could have retained enough EFW to explain their fall in $P_{Na}$; any extra water either was excreted in the urine or sweat or was turned into an isotonic saline as a result of a positive balance for $Na^+$. In the patients whose points fell below the line of identity, the amount of EFW given can be only a partial explanation for their fall in $P_{Na}$. These patients required a concurrent excretion of hypertonic $Na^+$ (+ $K^+$) and/or an occult source of EFW to achieve their observed fall in $P_{Na}$.

**TABLE 1.** Results from a Matched Case-Control Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Cases ($n = 37$)</th>
<th>Controls ($n = 111$)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Age, y</td>
<td>7 ± 6</td>
<td>7 ± 6</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Gender, number (%)</td>
<td>15 (41) F, 22 (60) M</td>
<td>45 (41) F, 66 (60) M</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Weight, kg</td>
<td>25 ± 18</td>
<td>28 ± 21</td>
<td>.4</td>
</tr>
<tr>
<td></td>
<td>Surgery, number (%)</td>
<td>6 (16)</td>
<td>6 (5)</td>
<td>.04</td>
</tr>
<tr>
<td>Water and sodium</td>
<td>$P_{Na}$</td>
<td>139 ± 3 → 133 ± 2 mM</td>
<td>140 ± 2 mM</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Decrease in $P_{Na}$, mmol</td>
<td>6 ± 3 in 19 ± 10 h</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>EFW, mL/kg/h</td>
<td>2 ± 2</td>
<td>1 ± 1</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td></td>
<td>$Na^+$, mmol/kg/h</td>
<td>0 ± 1</td>
<td>1 ± 1</td>
<td>.3</td>
</tr>
<tr>
<td></td>
<td>Positive water balance, ml/kg/h*</td>
<td>4 ± 5</td>
<td>2 ± 3</td>
<td>.02</td>
</tr>
<tr>
<td>IV-fluid regimen</td>
<td>Amount of fluid, ml/h</td>
<td>98 ± 77</td>
<td>47 ± 46</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td></td>
<td>% that received more than</td>
<td>73</td>
<td>23</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Main disease categories</td>
<td>GI disorders, number (%)</td>
<td>11 (30)</td>
<td>19 (17)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Neoplasia</td>
<td>8 (22)</td>
<td>14 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Respiratory infections</td>
<td>5 (14)</td>
<td>28 (23)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Renal disease</td>
<td>1 (3)</td>
<td>6 (5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Reason for elevated ADH</td>
<td>Disease, number (%)</td>
<td>5 (14)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Symptoms</td>
<td>23 (62)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>9 (24)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Hypovolemia</td>
<td>0 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Possible symptoms</td>
<td>Nausea, number (%)</td>
<td>10 (27)</td>
<td>3 (8)</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>2 (5)</td>
<td>11 (10)</td>
<td>.5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>25 (68)</td>
<td>46 (41)</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td>1 (3)</td>
<td>6 (5)</td>
<td>.7</td>
</tr>
<tr>
<td></td>
<td>Sensoryum changes</td>
<td>7 (19)</td>
<td>13 (12)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Data were available for all cases and 43 controls.
† As described by the formula of Holliday and Segar.\textsuperscript{8}
amount of intravenous fluid than recommended for maintenance on the basis of the formula of Holliday and Segar,8 the amount given was a contributing causative factor. The infusion of a large volume of saline was likely attributable to the belief that the ECF volume was contracted. For the group that did not have a recorded input of sufficient water to explain their fall in PNa (Fig 1, points below line of identity), one would suspect that they had an occult water intake (eg, ice chips, water residing in the lumen of the gastrointestinal tract after admission, electrolyte-free water generation by the kidney secondary to the excretion of hypertonic urine; open dots in Fig 2). For this latter mechanism, one needs the combination of an infusion of isotonic saline and the excretion of hypertonic urine.7 It is possible that this desalination process may have been triggered by the acute expansion of the ECF volume as a result of the administration of isotonic saline, because we could find recorded evidence that the ECF volume was contracted in only 10% of these patients. We emphasize that the clinical assessment of the degree of ECF volume contraction is a method of limited sensitivity and specificity.34–37

Dangers of Acute Hyponatremia

Previous studies have shown that children with acute hyponatremia have an appreciable risk for neurologic damage.5,6,38,39 With respect to the potential dangers of acute hyponatremia in our patient population, it is possible that the observed fall in PNa led to serious severe neurologic outcomes in 2 of 40 patients. One of these (Fig 1; fall in PNa of 14 mmol/L) had an underlying seizure disorder and had a convulsion during the hyponatremic period. This highlights the need to be more vigilant about the fall in PNa when an underlying medical condition places the patient at risk. We also emphasize a diagnostic caveat: that a seizure may raise the PNa transiently by an average of 13 mmol/L, masking the original degree of hyponatremia.40 The second patient (fall in PNa of 13 mmol/L from 142 to 128 mmol/L in 1.5 hours) had a cardiac arrest. Although she was resuscitated initially, she ultimately died. Postmortem examination revealed brain cell swelling. The high incidence of nausea and vomiting (Table 1) may indicate more cases of symptomatic hyponatremia; however, because these symptoms are also known to be potent stimuli of ADH release, this deduction is not possible from this retrospective study.

Rationale of the Choice of Intravenous Fluid: Hypotonic Versus Isotonic

The almost universal practice of the use of hypotonic fluids in children is based on calculations that linked energy expenditure to water and electrolyte losses, published nearly 50 years ago. Applying this formula results in the administration of large amounts of EFW, which then has to be excreted by the kidney. We believe that linking energy expenditure to water losses in hospitalized patients significantly overestimates the need for maintenance fluid. In a recent commentary,16 we reevaluated the factors used to calculate water and electrolyte requirements in Holliday and Segar’s original paper. Moreover, these calculations did not factor in the unpredictable effect of nonosmotic stimuli for ADH secretion in the acutely ill child, which can result in retention of water and hyponatremia.18 Our conclusion was that
the water requirements and the renal ability to excrete hypotonic urine were overestimated. Therefore, our general recommendation was that the PNa be measured once the ECF volume is expanded >10% (30 mL/kg); and if the PNa is <138 mmol/L, then do not infuse hypotonic fluids.16

The option of selecting isotonic rather than hypotonic for maintenance fluid in children has been advocated by some authors.6,41–43 In a recent publication, Moritz and Ayus43 drew attention to this idea, and our data support this position. This generally has not been accepted because of concerns about excessive administration of Na+ and the development of hyponatremia. The comparative studies in children, although few, do not support this perceived danger. In a randomized trial of different fluid protocols in children with meningitis, Powell et al20 compared a fluid-restricted group who received hypotonic saline with a fluid-deficit replacement plus maintenance regimen using predominantly isotonic solutions. Children in the isotonic group received an average of 6 mmol Na+/kg/day and had normal PNa levels, whereas those in the hypotonic group received an average of 2 mmol Na+/kg/day and became hyponatremic. Likewise, in the study by Gerigk et al18 of acutely ill children in which the median PNa was 136 mmol/L at the time of admission to hospital, those who were given isotonic fluid had a more rapid fall in their ADH levels than those who received hypotonic fluids.

Children who undergo surgical procedures are particularly at risk from hyponatremia because of the association between anesthetic agents and opiates and nonosmotic ADH secretion. Moreover, the syndrome of inappropriate ADH secretion has been frequently reported in association with spinal surgery.30,44 Burrows et al30 compared hypotonic with isotonic intravenous fluids in children who underwent surgery for scoliosis. Both groups had a fall in their PNa in the postoperative period, but the reduction was greater in those who received the hypotonic solution.

Patients who have findings of hyponatremia, with impaired excretion of EFW as a result of actions of ADH in the absence of obvious stimuli for ADH release (an ECF volume contraction of at least 8%), or either adrenal insufficiency or hypothyroidism are likely to be commonplace. We believe that hospital-acquired hyponatremia unnecessarily puts children at risk for the development of adverse neurologic events and is largely preventable. We suggest that the current recommendations for intravenous fluid therapy in hospitalized children be revised. Hypotonic fluids should not be used routinely in the intraoperative or postoperative period or when a patient has a PNa in the low-normal or distinctly hypotonic range (<138 mmol/L). In addition, boluses of isotonic saline should be given only when there are clear hemodynamic indications for that infusion.

Study Limitations

This study was retrospective and hence has the imperfections that characterize such studies. By evaluating every patient who arrived in our emergency department in a 3-month period, we attempted to minimize this limitation. Our actual incidence of hyponatremia is probably an overestimation because the PNa was measured in only ~10% of the total population, a group that had indications for this measurement. In addition to these limitations, there was the problem of not measuring urine electrolytes and plasma ADH levels. Also, some of the patients and especially those who received insufficient EFW to explain their fall in PNa could have had an occult source of water. Occult sources of water include water in the gastrointestinal tract that was not absorbed before the first measurement of the PNa, the use of ice chips, or a parent’s giving his or her child a drink without informing the nurse so that there is no record of that input in the hospital chart. We think that a prospective study to answer some of the obvious questions would be helpful.

CONCLUSIONS

The development of hyponatremia is unacceptably high in hospitalized children. This is attributable in large part to the administration of excessive amounts of water as hypotonic saline in situations in which ADH is secreted for nonosmotic reasons. The original guidelines for maintenance fluid may not be applicable in an era when the complexity and the severity of illness seen in hospitalized children who receive intravenous fluid therapy has radically changed (eg, leukemia, complex congenital heart disease) and irregularities of ADH secretion are more likely to be commonplace. We believe that hospital-acquired hyponatremia unnecessarily puts children at risk for the development of adverse neurologic events and is largely preventable. We suggest that the current recommendations for intravenous fluid therapy in hospitalized children be revised. Hypotonic fluids should not be used routinely in the intraoperative or postoperative period or when a patient has a PNa in the low-normal or distinctly hypotonic range (<138 mmol/L). In addition, boluses of isotonic saline should be given only when there are clear hemodynamic indications for that infusion.

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