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High Antidiuretic Hormone Levels and Hyponatremia in Children With Gastroenteritis

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ABSTRACT. *Objectives.* Nonosmotic antidiuretic hormone (ADH) activity can cause severe hyponatremia during involuntary fluid administration. We looked for evidence of this before and during intravenous (IV) fluid administration in children treated for gastroenteritis.

Methodology. In this prospective observational study, plasma ADH, electrolytes, osmolality, and glucose were measured in 52 subjects before (T_0) and 4 hours after (T_4) starting 0.45% saline + 2.5% dextrose and subsequently when indicated. Hormonal markers of stress were measured at T_0 . Urine samples were collected to measure electrolytes and osmolality.

Results. The nonosmotic stimuli of ADH secretion that we identified were vomiting (50 of 52), dehydration (median: 5%; range: 3–8%), hypoglycemia (2 of 52), and raised hormonal markers of stress (mean \pm SD: cortisol, 1094 ± 589 nmol/L; reverse triiodothyronine, 792 ± 293 pmol/L). At T_0 , half the children were hyponatremic (plasma sodium concentration of <135 mmol/L; $n = 27$). The median plasma ADH concentration at T_0 was significantly elevated (median: 7.4 pg/mL; range: <1.9 –85.6 pg/mL). ADH was high in both hyponatremic and normonatremic children and remained high at T_4 in 33 of the 52 children, 22 of whom were concurrently hyponatremic. At T_4 , mean plasma sodium concentration was unchanged in the hyponatremic children but was 2.6 mmol/L (± 2.0) lower in those who were initially normonatremic. Urine tonicity was high compared with 0.45% saline in 16 of 19 children at baseline and in 20 of 37 children after 3 to 12 hours of IV fluids.

Conclusions. Nonosmotic stimuli of ADH secretion are frequent in children with gastroenteritis. Their persistence during IV-fluid administration predisposes to dilutional hyponatremia. The use of hypotonic saline for deficit replacement needs to be reassessed. *Pediatrics* 2005;116:1401–1407; ADH, hyponatremia, sodium, gastro-

enteritis, fluid therapy, infusions intravenous, dehydration.

ABBREVIATIONS. IV, intravenous; ADH, antidiuretic hormone; RRP, rapid-replacement protocol; SRP, slow-replacement protocol; rT3, reverse triiodothyronine; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyrotropin; CV, coefficient of variation; SDS, standard deviation score.

Despite the widespread acceptance and recommendation of oral rehydration solutions for rehydration of children with mild to moderate dehydration secondary to gastroenteritis,^{1–3} recent audits of clinical practice have shown that intravenous (IV) fluids are used frequently in industrialized countries.^{4–6} Although isotonic solutions are recommended for acute volume expansion for shock,^{1–3,7} hypotonic fluids are often used for IV replacement of fluid deficit in children with gastroenteritis⁷ and have been recommended by some groups even when rapid-replacement regimes are used,^{2,3,8} in which the estimated deficit or a fixed amount of fluid is infused intravenously over 2 to 4 hours. Gastroenteritis in developed countries is usually a benign, self-limited disease; however, severe hyponatremia and cerebral edema resulting in death or permanent neurologic impairment have been recorded during IV-fluid therapy^{9,10} and, indeed, in children and adults during excessive oral intake.^{11,12} Such rare but catastrophic outcomes have been attributed to the use of hypotonic saline solutions and/or the rate of fluid administration. The apparent inability of these children to excrete a free-water load suggests that antidiuretic hormone (ADH) is acting despite low plasma osmolality.

In health, maintenance of plasma sodium and osmolality within narrow limits is achieved by thirst-directed fluid intake and varying renal water excretion, primarily via ADH activity.¹³ ADH limits renal water excretion, with maximal antidiuresis achieved at plasma concentrations of ADH between 3 and 5 pg/mL.¹³ Although ADH levels are usually closely linked to plasma osmolality, a number of nonosmotic stimulants of ADH secretion may disrupt this link. These stimulants include intravascular volume depletion,^{13,14} nausea and vomiting,¹³ stress,¹⁵ and hypoglycemia,¹⁶ some or all of which may be operative in gastroenteritis. Nonosmotic ADH activity during parenteral fluid administration could lead to dilutional hyponatremia, particularly if hypotonic fluids

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Drs Neville and Walker had the original idea and initiated and designed the study; Dr Neville implemented the study, performed the statistical analysis, and drafted the report; Dr Walker contributed to the analysis of the data and the writing of the manuscript; Dr Verge contributed to the study design and data analysis and was involved in revising the article critically; and Dr O'Meara participated in the acquisition of data and was involved in revising the article critically.

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are used. This mechanism is thought to underlie the well-documented development of hyponatremia in children and adults during postoperative fluid administration^{17,18} and could be operative in children during IV rehydration for gastroenteritis.

To explore this, we looked for nonosmotic stimulants and biochemical measures of ADH activity in a prospective observational study of children admitted through the emergency department at Sydney Children's Hospital who had a presumptive diagnosis of gastroenteritis and in whom a decision to treat with IV fluids had been made by their treating physician.

METHODS

This prospective observational study was conducted at Sydney Children's Hospital between the months of August and October 2001, corresponding to the annual peak incidence of rotavirus infection.¹⁹ Children aged between 6 months and 14 years with a presumptive diagnosis of gastroenteritis were eligible for enrollment in the study only after a decision to treat with IV fluids had been made by their treating physician, independent of this study. The reasons recorded for this decision were the combination of dehydration judged on clinical grounds and either continued vomiting or inadequate intake of oral fluids in the emergency department. Children were excluded from the study if they had a known abnormality of ADH secretion, nephrogenic diabetes insipidus, pituitary or hypothalamic disease, acute or chronic lung disease, or renal disease or were receiving drugs known to stimulate ADH secretion. The study was approved by the South Eastern Area Research Ethics Committee, and informed consent was obtained from a parent/guardian of each child before inclusion.

During the study period, 827 children presented to the emergency department with gastroenteritis, of whom 36% (304 of 827) received IV fluids. To be included in the analysis, blood had to be collected for the measurement of plasma sodium, osmolality, and ADH before (T_0) and 4 hours after (T_4) IV fluids were started. The T_4 measurement corresponded to completion of the rapid-replacement protocol (RRP), 1 of the 2 rehydration protocols in use in this emergency department (see below). Of 70 children who were randomly approached and enrolled, measurements of plasma sodium, osmolality, and ADH were obtained successfully at both T_0 and T_4 in 52 (31 boys). The median age of the 52 children was 3.2 years (range: 0.7–12.8 years) and their mean height, weight, and BMI measurements were average for age (data not shown). Stools for culture and rotavirus antigen testing were obtained from 22 children. In 4 children, no pathogen was isolated, 17 were positive for rotavirus antigen, and 1 was positive for *Campylobacter jejuni*.

In accordance with the Sydney Children's Hospital guidelines for the use of IV fluids for gastroenteritis, all children received 0.45% saline with 2.5% dextrose administered according to either the RRP (10 mL/kg per hour for 4 hours) or the slow-replacement protocol (SRP; maintenance fluids²⁰ + estimated dehydration as a percentage of body weight replaced over 24 hours). The decision to use the RRP or SRP was at the discretion of the treating physician except that the RRP carries its own exclusion criteria such that it cannot be used in children <6 months age, who are estimated to be >8% dehydrated, or whose pretreatment plasma sodium concentration is <130 mmol/L. Of the 52 children, 40 completed 4 hours of the RRP, of whom 9 continued IV fluids according to the SRP for clinical indications. Of the 12 who received the SRP, 6 were changed from RRP to SRP within 1 hour of starting IV fluids because their plasma sodium concentrations were <130 mmol/L. These children were classified as having received the SRP.

Potential Nonosmotic Stimulants of ADH Activity

Details of the illness before presentation were recorded. To examine whether children who were particularly underweight for height might be at greater risk of nonosmotic ADH activity, the BMI standard deviation score (SDS) was assessed. The degree of dehydration at presentation was estimated by using standard clinical measures.²¹ Weight at discharge from hospital measured on the same scales as the admission weight was also recorded as an additional measure of initial dehydration in 47 of 52 children.

To look for hypoglycemia (plasma glucose \leq 2.6 mmol/L), blood glucose was measured with each blood sample. As proxy biochemical measures of the stress posed by gastroenteritis, serum concentrations of cortisol and reverse triiodothyronine (rT3), free triiodothyronine (fT3), free thyroxine (fT4), and thyrotropin (TSH) were measured at T_0 .

Biochemical Measures of ADH Activity

Plasma sodium, osmolality, and ADH were measured in all blood samples collected at T_0 and T_4 and in subsequent samples obtained when clinically indicated. To determine if the initial plasma sodium concentration was an indicator of the risk of subsequent dilutional hyponatremia, the response to IV fluids was analyzed according to whether the children were normonatremic or hyponatremic at T_0 . Hyponatremia was defined as a plasma sodium concentration of <135 mmol/L, and normonatremia was defined as a plasma sodium concentration of 135 to 145 mmol/L. A change in plasma sodium concentration of \geq 2 mmol/L was considered to be biochemically significant because it exceeds the coefficient of variation (CV) of the assay for the laboratory reference range of 135 to 145 mmol/L (CV: 1.3–1.5%).

Urine-sample collection via urine bag in incontinent children and clean-catch specimens in toilet-trained children was attempted and timed as closely as possible to the blood sampling. Urinary sodium concentration, tonicity (urinary sodium plus potassium concentration), and osmolality were determined in all urine samples that were obtained. Fractional excretion of sodium was calculated when possible by using the T_0 and T_4 plasma concentrations of sodium and creatinine. The ratio of urinary potassium to sodium was calculated also.

Laboratory Methods

For the measurement of ADH, blood was collected in a lithium heparin tube that was placed immediately in ice. The plasma was separated immediately from each sample and stored at -20°C for later assaying. Plasma ADH was measured in duplicate by a commercially available protein-binding radioimmunoassay kit (Nichols Institute Diagnostic, San Juan Capistrano, CA), with an interassay CV of 12% to 15% and an intraassay CV of 10.3%. The lower limit of detectability of the assay was 1.9 pg/mL. rT3 was measured by radioimmunoassay (Biodata; Biochem Immuno Systems, Rome, Italy) with an interassay CV of 5.7% to 11.8%. Plasma and urinary sodium and potassium were measured by standard automated methods using ion-selective electrodes, osmolality using freezing-point depression, and plasma glucose using an oxygen-rate method. Serum cortisol, fT4, fT3, and TSH were measured by standard automated methods.

Statistical Analysis

All statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS 11.0; SPSS Inc, Chicago, IL). Means between groups were compared by independent t tests, and paired variables were compared by paired sample t tests. Medians were compared by the Mann-Whitney U test, and changes over time were compared by the Wilcoxon signed-rank test. Categorical data were analyzed by using cross tabulation and the χ^2 test. Statistical significance was defined as a P value of <.05.

RESULTS

Nonosmotic Stimuli of ADH Secretion at Presentation

Vomiting

Vomiting was a presenting symptom in 96% of the children. Twenty-two children (42%) were reported to have a vomiting illness only before presentation, 28 (54%) had vomiting and diarrhea, and 2 (4%) had diarrhea only. Continued vomiting was the reason for prolongation of IV fluids beyond 4 hours in 8 of 9 children who completed 4 hours of the RRP but continued according to the SRP.

Dehydration

The clinical estimate of extracellular fluid volume contraction ranged between 3% and 8% (median:

5%). It was similar in those treated with RRP and SRP and did not correlate with the plasma sodium concentration at T_0 (data not shown). In keeping with the mild to moderate degree of dehydration estimated, comparison of the weights at admission and discharge showed a mean gain of $1.3\% \pm 2.3\%$ (range: -2.7% to 7.9%); however, this measurement was obtained a variable period of time after cessation of IV fluids and does not take into account continued losses or varying oral intake.

Hypoglycemia

Hypoglycemia was documented in 2 (4%) of the 52 children at T_0 who had plasma glucose levels of 2.3 and 2.5 mmol/L. The children were 5.5 and 2.1 years old, respectively, and their BMI SDSs on admission were -0.47 and -2.11 , respectively. The hypoglycemia resolved once dextrose-containing IV fluids were started and subsequent investigations excluded a second pathology.

Hormonal Markers of Stress

The mean serum cortisol at T_0 was 1094 ± 589 nmol/L (range: 223–2702 nmol/L), compared with the 8 AM reference range of 155 to 599 nmol/L. The serum concentrations of FT4, FT3, and TSH fell within the laboratory reference ranges (data not shown); however, the mean serum concentration of rT3 was 792 ± 293 pmol/L, with 93% of readings falling above the laboratory reference range (170–450 pmol/L). The serum concentrations of the hormones measured were similar in the children who were normonatremic and hyponatremic at T_0 (data not shown).

Biochemical Measures of ADH Activity at Baseline (T_0)

The mean plasma sodium concentration at T_0 was 134 ± 3.8 mmol/L (range: 127–141 mmol/L) and the mean plasma osmolality was 281 ± 8.3 mOsm/kg. Twenty-seven of the children (52%) were hyponatremic (mean: 131 ± 2.5 mmol/L) (Table 1) and in 9 (17%) of the 52 children the plasma sodium concentration was <130 mmol/L. Children who were hyponatremic at T_0 had a longer illness before presentation than those who were normonatremic (median: 2 days [range: <24 hours to 5 days] vs <24 hours [<24 hours to 7 days]; $P = .03$); however, there was

no significant difference in age, gender, BMI SDS, percent dehydration, or rotavirus positivity between the groups.

The median plasma ADH concentration at T_0 for the 52 children was 7.4 pg/mL (range: <1.9 –85.6 pg/mL) and was significantly lower in hyponatremic versus normonatremic children ($P < .001$) (Table 1). There was no correlation between plasma ADH concentration and plasma sodium concentration (Fig 1A) or plasma osmolality (Fig 1 B and C) in either hyponatremic (Fig 1B) or normonatremic children (Fig 1C).

Obtaining urine samples that were appropriately paired with blood samples proved difficult because of oliguria, leakage from collection bags in incontinent infants, and the mixing of stool and urine in continent children. The first urine was passed at a median of 2.8 hours after starting IV fluids (range: -1.0 to 12.0 hours). There was no correlation between the time that the first urine was passed and the plasma concentrations of sodium or ADH (data not shown).

In the 19 children (13 hyponatremic) whose first urine sample was passed and obtained within 2 hours of T_0 (median: 0.2 hours; range: -1.0 to 1.8 hours), the median urinary sodium concentration was 79 mmol/L (range: <10 –171 mmol/L), the median potassium concentration was 77 mmol/L (range: 6–247 mmol/L), the median potassium/sodium ratio was 1.2 (range: 0.3–9.6), the median tonicity (sodium + potassium concentration) was 161 mmol/L (range: 22–336 mmol/L), and the median osmolality was 991 mOsm/kg (range: 125–1283 mOsm/kg) (Fig 2). The median fractional excretion of sodium was 3.08 (range: 0.37–17.38). The urine was hypertonic compared with the child's plasma in 11 (58%) of 19 children and compared with the IV fluid infused (tonicity: 75 mmol/L) in 16 (84%) of 19 children (Fig 2B).

Biochemical Measures of ADH Activity After 4 Hours of IV Fluids

The response of plasma sodium, osmolality, and ADH was no different if the children receiving RRP or SRP were analyzed separately or together. Moreover, multivariate analysis showed that only initial normonatremia ($P < .001$) and not rate of fluid ad-

TABLE 1. Plasma Sodium, Osmolality and ADH at Baseline (T_0) and After 4 Hours of IV Rehydration (T_4) in 52 Children With Gastroenteritis According to Whether They Were Hyponatremic (Plasma Sodium < 135 mmol/L) or Normonatremic (Plasma Sodium Between 135 and 145 mmol/L) at T_0

	Hyponatremic at T_0 (n = 27)	Normonatremic at T_0 (n = 25)	P
Sodium, mmol/L, mean (SD)			
T_0	131 (± 2.5)	138 (± 1.6)	
T_4	132 (± 2.9)	135 (± 2.2)†	
Change in sodium, mmol/L, mean (SD)	0.3 (± 2.1)	-2.6 (± 2.0)	$< .001$
Osmolality, mOsm/kg, mean (SD)			
T_0	275 (± 6.8)	286 (± 5.5)	$< .001$
T_4	272 (± 5.7)‡	280 (± 5.3)†	$< .001$
ADH, pg/mL, median (range)			
T_0	5.9 (<1.9 –30.8)	14.8 (<1.9 –85.6)	$< .001$
T_4	2.9 (<1.9 –11.0)†	4.6 (<1.9 –15.7)†	$< .04$

† $P < .001$ (T_4 versus T_0).

‡ $P = .04$ (T_4 versus T_0).

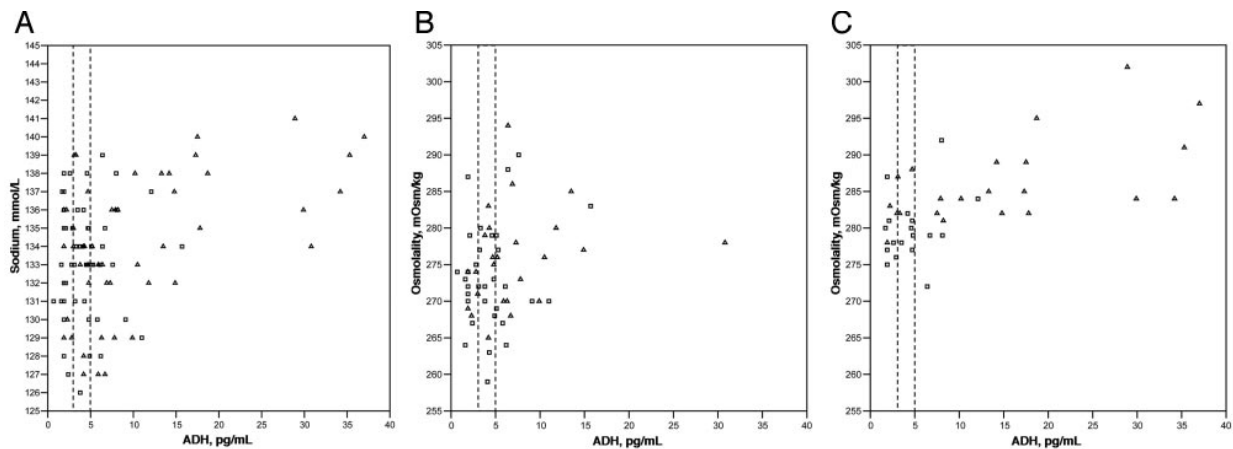


Fig 1. Plasma ADH versus plasma sodium (A) and osmolality (B and C) in hyponatremic (plasma sodium concentration of <135 mmol/L; B) and normonatremic (plasma sodium concentration of 135–145 mmol/L; C) children at baseline (Δ) and 4 hours after IV fluids (\square). Three normonatremic children (not shown) had baseline plasma ADH concentrations of 68.1, 81.6, and 85.6 pg/mL associated with plasma osmolalities of 284, 289, and 289 mOsm/kg, respectively. The area between the 2 dotted lines indicates the range of ADH levels above which maximal antidiuresis occurs, as determined in experimental situations.¹³

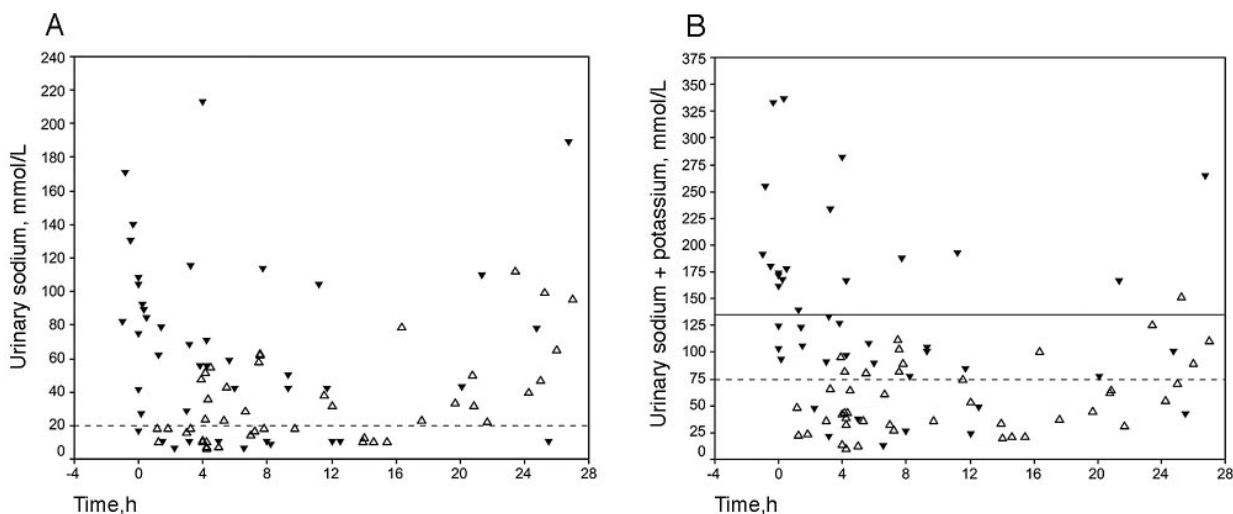


Fig 2. Urinary sodium concentrations (A) and tonicity (urinary sodium + potassium concentration; B) for all urine samples ($n = 90$) obtained from the 52 children during the first 28 hours after starting IV rehydration according to whether the urinary osmolality in the same specimen was >600 mOsm/kg (∇) or <600 mOsm/kg (Δ). A, The dotted line corresponds to the urinary sodium concentration associated with maximal renal reabsorption of sodium. B, The dotted line corresponds to the tonicity of 0.45% saline + 2.5% dextrose, and the solid line corresponds to the average tonicity of plasma at T_0 (determined by a plasma sodium concentration of 135 mmol/L).

ministration ($P = .17$) made an independent contribution to change in plasma sodium. Therefore, the results of the 52 children are presented together.

Plasma Sodium and Osmolality

After 4 hours, the mean plasma sodium concentration for the 52 children had decreased to 133 ± 3.1 mmol/L (range: 126–139 mmol/L; $P = .002$ versus T_0). This decrease was the result of a mean decrease of 2.6 ± 2.0 mmol/L in the normonatremic children, whereas the hyponatremic children had no change in their plasma sodium (Table 1). In the normonatremic group, plasma sodium concentration decreased by ≥ 2 mmol/L in 76% (19 of 25) compared with 19% (5 of 27) in the hyponatremic group ($P < .001$). In 3 of the children in the normonatremic group, the decrease was ≥ 5 mmol/L. As expected, plasma osmolality decreased during treatment (Table 1).

Plasma ADH Levels

Plasma ADH concentrations decreased in both the hyponatremic and normonatremic groups during the first 4 hours of fluid therapy but remained significantly higher in the initially normonatremic group (Table 1). At T_4 , plasma ADH concentration remained within or above the range associated with maximal antidiuresis (3–5 pg/mL¹³) in 33 of the 52 children (Fig 1 B and C), 22 of whom had concurrent plasma sodium concentrations of <135 mmol/L (Fig 1B).

Urinary Sodium, Osmolality, and Tonicity

Urine samples were obtained from 37 children between 3.2 and 12 hours (median: 5 hours) after starting IV fluids. The median urinary sodium was 36 mmol/L (range: <10–213 mmol/L), median po-

tassium was 30 mmol/L (range: 3–96 mmol/L), median osmolality was 534 mOsm/kg (range: 73–1350), and median tonicity was 65 mmol/L (range: 10–282), with the tonicity higher than the infused fluid in 20 of 37 children (Fig 2B). The median fractional excretion of sodium was 2.2 (range: 0.04–13.08), and the ratio of urinary potassium/sodium was 0.98 (range: 0.18–4.33).

Hyponatremia had persisted or developed at T_4 in 24 (65%) of 37 children. Despite this, the median urinary sodium concentration was 39 mmol/L (range: <10–71 mmol/L) and exceeded 20 mmol/L in 15 of 24 children, suggesting an inability to conserve sodium appropriately. The concurrent median urinary osmolality was 611 mOsm/kg (range: 188–1191 mOsm/kg). The 13 (35%) of 37 children with urine samples who remained or became normonatremic at T_4 had similar median urinary sodium concentrations (median: 23 mmol/L; range: <10–213 mmol/L); however, the median urinary osmolality of 450 mOsm/kg (range: 73–944 mOsm/kg) was lower ($P = .05$), suggesting that they were better able to excrete free water.

ADH Activity During Prolonged Fluid Administration

Twenty-one children (12 receiving SRP, 9 receiving RRP) received >4 hours of IV rehydration. During the first 4 hours of IV fluids, the plasma sodium concentration had decreased by 1.0 ± 2.6 mmol/L to a mean of 132 ± 3.9 mmol/L, and the concurrent mean plasma osmolality and median ADH concentrations at T_4 were 272 ± 6.0 mOsm/kg and 4.6 pg/mL (range: <1.9–15.7 pg/mL), respectively. Additional blood and urine samples were obtained from these children between 8 and 60 hours after T_0 . Biochemistry was available after 24 hours in 15 of 21 subjects, in whom the mean plasma sodium concentration was 135 ± 3.0 mmol/L (range: 129–140 mmol/L) and <135 mmol/L in 6 (40%) of 15. The mean plasma osmolality was 275 ± 6.7 mOsm/kg. The median plasma ADH concentration was 3.5 pg/mL (range: <1.9–7.8 pg/mL; $n = 14$) and was within or above the range associated with maximal antidiuresis in 10 (71%) of the children.

To gauge the potential for clinically significant nonosmotic ADH activity in this population, each individual's longitudinal biochemical data were studied. Twenty-nine percent (6 of 21) of the children who received prolonged IV fluids had persistent sig-

nificant hyponatremia (sodium concentration of ≤ 131 mmol/L) or decreases in plasma sodium concentration of ≥ 4 mmol/L to <135 mmol/L associated with an inappropriately high urinary sodium content (range: 27–189 mmol/L) and urine osmolality higher than plasma osmolality (range: 402–1191 mOsm/kg), suggesting that they were at risk for dilutional hyponatremia. The plasma and urinary abnormalities were documented to persist for a median of 38 hours (range: 20–46 hours). Plasma ADH levels were between 3.8 and 15.7 pg/mL at T_4 and remained raised (between 3.6 and 6.2 pg/mL) in the 3 of 6 in whom it was measured 8 to 36 hours after starting IV fluids. One such child's results are shown in Table 2. Another child who had received only 4 hours of the RRP had similar biochemistry after 4 hours.

Comparing these 6 children with the remaining 15 of 21 who received prolonged fluids, no clinical or biochemical parameters emerged that would allow identification of those at risk. All 6 children had stool cultures positive for rotavirus, and 4 completed 4 hours of the RRP. The median duration of illness before presentation was shorter in the children affected (median: 1 day [range: <24 hours to 2 days] vs 2 days [<24 hours to 7 days]; $P = .045$), but there was no difference in the clinical assessment of percent dehydration ($P = .27$), age ($P = .62$), or BMI SDS ($P = .68$). They had higher median concentrations of urea (6.9 mmol/L [range: 5.5–9.3] vs 4.9 mmol/L [range: 2.4–7.5]; $P = .02$) and ADH (16.1 pg/mL [range: 5.9–81.6] vs 4.2 pg/mL [range: <1.9–17.5]; $P = .008$) but no difference in baseline plasma sodium ($P = .73$), bicarbonate ($P = .27$), creatinine ($P = .79$), cortisol ($P = .50$), or rT3 ($P = .86$).

DISCUSSION

This study suggests that osmotically inappropriate ADH activity is a frequent phenomenon in children who present with symptoms of gastroenteritis but that its severity and duration are variable. It follows that the administration of fluids, not directed by thirst, has the potential to cause dilutional hyponatremia with its attendant risks. Our data suggest that hypotonic saline solutions are inappropriate for replacement of acute volume depletion and support the need for greater persistence with oral rehydration for gastroenteritis in children.

Although the median plasma ADH concentrations

TABLE 2. Evidence of Clinically Significant Nonosmotic ADH Secretion in a 5-Year-Old Child With Rotavirus-Positive Gastroenteritis

Time, h	Plasma Sodium, mmol/L	Plasma Osmolality, mOsm/kg	Urine Sodium, mmol/L	Urine Tonicity, mmol/L	Urine Osmolality, mOsm/kg	Plasma ADH, pg/mL
0	129	270				9.9
4	129	270				11.0
12	129	266	42	84	920 (first urine passed)	4.8
24	129	259	78	100	752	6.2
39	130	271	140	161	569	4.7

The rate of infusion of 0.45% saline + 2.5% dextrose was changed from the rapid infusion rate to the standard infusion rate (maintenance + 5% over 24 hours) within the first 2 hours when the results of the initial plasma sodium concentration became known (≤ 130 mmol/L). The infusion rate was reduced further to two thirds that of maintenance at 15 hours and half that of maintenance at 30 hours because of persistent hyponatremia.

were higher in the normonatremic than hyponatremic children (Table 1), as would be predicted by the close link between plasma osmolality and ADH secretion, there was no correlation between plasma concentrations of ADH and either plasma sodium or osmolality. Concentrations were within or above the range associated with maximal antidiuresis even in children with hyponatremia and low plasma osmolality (Table 1; Fig 1), demonstrating the presence of nonosmotic stimulants of ADH secretion. The 3 major nonosmotic stimulants of ADH secretion identified in this study were dehydration, vomiting, and stress. None of the children studied was judged to be severely dehydrated (>8%), a situation in which baroreceptor stimulation of ADH to preserve intravascular volume takes precedence over osmotic regulation of ADH production in experimental situations.¹⁴ With the mild to moderate degree of volume contraction observed in our children, osmotic regulation of ADH secretion should have been preserved although the osmotic threshold at which ADH secretion is suppressed may have been lower,¹⁴ as has been suggested previously in dehydrated hyponatremic children with shigellosis.²²

Vomiting and stress, both potent nonosmotic stimuli of ADH secretion,^{13,15} were prominent in our study group. Vomiting was a presenting symptom in 96% of the children and the main reason for continuing IV fluids beyond 4 hours. Our hormonal studies suggest that gastroenteritis constitutes a significant stress. The mean rT_3 concentration at T_0 was approximately double the upper limit of the reference range and was consistent with sick euthyroid syndrome.²³ The plasma concentrations of cortisol at T_0 also were well above the laboratory reference range and higher than is usually seen during adrenocorticotropin stimulation.²⁴ Hypoglycemia at presentation was uncommon (4%) and responded to the dextrose content of the IV fluid. Its contribution to nonosmotic ADH secretion is likely to have been minimal.

Hyponatremia at presentation was more frequent than has been reported previously,^{6,25} with approximately half of the children having a plasma sodium concentration below the reference range. The type of oral fluid ingested before the start of IV fluids was not recorded systematically, but tended to consist of water or dilute apple juice rather than the recommended glucose- and electrolyte-containing oral rehydration solutions. Hypotonic oral fluids therefore would have provided a source of electrolyte-free water, which in the face of osmotically unregulated ADH activity may have contributed to the hyponatremia documented. Sodium loss in the stools may also have been a factor in children with significant diarrhea. Our study was conducted during a time of high prevalence of rotavirus gastroenteritis,¹⁹ and rotavirus stools have been demonstrated to have a sodium content of between 30 and 50 mmol/L.²⁶

The urinary sodium concentration at presentation and during IV-fluid administration was surprisingly high (Fig 2A). Determinants of the urinary sodium concentration include dietary intake, glomerular filtration rate, and hormonal influences including aldosterone and natriuretic peptides. In the presence of

normal renal function, the expected renal response to hypovolemia, partly mediated by aldosterone, is to retain sodium with urinary concentrations of <20 mmol/L.^{27,28} In the children we studied, the degree of dehydration assessed would predict normal renal function; plasma concentrations of creatinine were normal for age in all children at baseline and subsequently (data not shown), and the fractional excretion of sodium in those for whom it could be calculated was not suggestive of prerenal failure. In the 19 children for whom analysis of a urine sample within 2 hours of starting rehydration was possible, the urine was concentrated as expected, but the median urinary sodium concentration was approximately that of the fluid infused, despite hyponatremia in 68% (13 of 19) of the children. Among those in whom a urine sample was collected between 3 and 12 hours after starting IV fluids, the urinary sodium concentration was >20 mmol/L in 15 of 24 children who remained or became hyponatremic at T_4 . There are few data on urinary electrolytes in either healthy children or those with gastroenteritis. One study in healthy school-aged children reported that urinary sodium concentrations average 140 to 150 mmol/L, with little variation throughout a 24-hour period,²⁹ compared with which our children were able to retain sodium. Urinary sodium concentrations of <20 mmol/L have been reported in severely hyponatremic but not normonatremic Bangladeshi children with shigellosis,²² although the corresponding urinary osmolalities approximated those of plasma, suggesting that the urinary volumes (and therefore excretion of sodium) may have been significant. The ratio of urinary potassium/sodium has been observed to decrease in infants with gastroenteritis during oral rehydration, and a ratio of >2 was reported to indicate the effect of aldosterone favoring sodium over potassium retention.³⁰ In our study population, although the median urinary potassium concentration in urine samples collected at 3 to 12 hours was approximately half that collected within 2 hours of starting IV fluids, the ratio of potassium/sodium remained at ~1, which we interpret as additional evidence that there was an obligatory loss of sodium. An explanation for the apparent obligate loss may lie with dietary factors: the dietary content of sodium has an impact on renal sodium resorption³¹ such that it is enhanced by a low-sodium diet, and acute starvation (such as might occur during gastroenteritis) is associated with natriuresis.³²

In the face of an obligate urinary sodium loss, continued limitation of water excretion by nonosmotic ADH activity has the potential to cause dilutional hyponatremia. Although plasma ADH concentrations fell after the start of IV fluids, they were still within or above the level associated with maximal antidiuresis after 4 hours in the majority of children. Consistent with this, there was a significant decrease in plasma sodium and osmolality at T_4 in the children who were normonatremic initially and a decrease to below the reference range of plasma osmolality in the majority of those who were initially hyponatremic, signifying that the osmotic regulation of ADH activity continued to be overridden. As ad-

ditional evidence for this conclusion, the children who remained or became normonatremic at T_4 were passing more dilute urine than those who remained or became hyponatremic, suggesting that the primary problem in the latter group was an inability to excrete a water load under the influence of ADH.

It could be argued that the unfavorable biochemical changes observed during a period of IV-fluid administration limited to 4 hours are of little clinical significance. The same cannot be said, however, when prolonged hypotonic fluid therapy is used. We found biochemical evidence of potentially significant dilutional hyponatremia associated with raised plasma concentrations of ADH in 29% of the children who received >4 hours of IV hypotonic saline. Moreover, no clinical or biochemical parameters emerged that would be useful at the bedside to identify children at particular risk. The adverse effects of nonosmotic ADH activity would be best avoided with the use of appropriate oral rehydration regimes, although it should be noted that non-thirst-directed oral intake also may be associated with dilutional hyponatremia.^{11,12} As has been suggested,¹⁰ if IV volume expansion is used, then use of isotonic fluids should decrease the risk of dilutional hyponatremia because of the relatively lower volume of electrolyte-free water presented.^{10,17} In keeping with this, the decreases in plasma sodium that we observed have not been reported when isotonic solutions are used in RRP. ^{25,33} Thus, our data suggest that the use of hypotonic saline solutions in childhood gastroenteritis needs to be reassessed.

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