Symptomatic Hyponatremia During Treatment of Dehydrating Diarrheal Disease With Reduced Osmolarity Oral Rehydration Solution

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Context In May 2002, the World Health Organization and the United Nations Children's Fund recommended that the formulation of oral rehydration solution (ORS) for treatment of patients with diarrhea be changed to one with a reduced osmolarity and that safety of the new formulation, particularly development of symptomatic hyponatremia, be monitored.

Objective To measure the rates of symptomatic hyponatremia during treatment of patients with diarrhea with reduced osmolarity ORS.

Design, Settings, and Patients A phase 4 trial conducted at the Dhaka hospital (December 1, 2002-November 30, 2003) and Matlab hospital (February 2, 2003-January 31, 2004) of the International Centre for Diarrhoeal Disease Research Bangladesh: Centre for Health and Population Research, Dhaka, Bangladesh. All patients admitted with uncomplicated watery diarrhea were treated with the newly recommended ORS and monitored. Patients developing neurological symptoms (seizure or altered consciousness) were transferred to the special care ward for treatment and investigated to identify the cause of the symptoms. Patient records of the Dhaka hospital were reviewed during the previous year when the old ORS formulation was used.

Intervention Reduced osmolarity ORS.

Main Outcome Measure Incidence rate of symptomatic hyponatremia in a 1-year period.

Results A total of 53 280 patients, including 22 536 children younger than 60 months, were monitored at the Dhaka and Matlab hospitals. Twenty-four patients, none older than 36 months, developed seizures or altered consciousness associated with hyponatremia, with an overall incidence rate of 0.05% (95% confidence interval [CI], 0.03%-0.07%) at the Dhaka hospital and 0.03% (95% CI, 0.01%-0.09%) at the Matlab hospital. During the previous year, 47 patients at the Dhaka hospital had symptoms associated with hyponatremia, for an estimated incidence rate of 0.10% (95% CI, 0.07%-0.13%). The reduction in the rates was statistically significant (odds ratio, 0.50; 95% CI, 0.29-0.85; $P = .009$).

Conclusion The risk of symptoms associated with hyponatremia in patients treated with the reduced osmolarity ORS is minimal and did not increase with the change in formulation.

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BEGINNING IN 1978, THE WORLD Health Organization (WHO) and the United Nations Children's Fund (UNICEF) recommended the use of a single formulation (sodium, 90 mEq/L; potassium, 20 mEq/L; chloride, 98 mEq/L; citrate, 290 mg/dL; glucose, 2000 mg/dL [111 mmol/L]; and osmolarity, 311 mOsm/L) of oral rehydration solution (ORS) for prevention and treatment of dehydration from diarrheal diseases due to any cause, including cholera, irrespective of patient's age.[1] The use of this ORS contributed to the dramatic global reduction in deaths from diarrheal diseases since that time.[2] The main limitation of this ORS, however, is that it neither reduces stool volume nor diarrhea duration,[3] 2 factors that are considered important for its acceptance by mothers and health care workers. There has also been concern that the solution, which

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is slightly hyperosmolar relative to plasma, might induce development of hypernatremia or an osmotically driven increase in stool output, especially in infants and young children.[4-6] For this reason, pediatricians in some developed countries recommended that the sodium content of ORS be reduced to 60 mEq/L, with a total osmolarity of 250 mOsm/L.[7] (In the United States, the leading brands have an even lower sodium and a higher glucose concentration, and therefore do not conform to the WHO recommendations.)

Recent efforts to improve the efficacy of ORS have focused on solutions with reduced osmolarity (range of sodium, 60-75 mEq/L and range of glucose, 1351-1622 mg/dL [75-90 mmol/L]).[8] These solutions generally preserve the 1:1 molar ratio of sodium to glucose that is crucial for efficient cotransport of sodium but present a lower osmolar load to the intestinal tract than the old formula did. Animal[9] and human studies[10-13] indicate that such solutions might be better designed for optimal water and electrolyte transport into the blood stream. In these intestinal perfusion studies,[10-13] solutions with reduced osmolarity have been demonstrated to have improved net water absorption and equivalent net sodium absorption compared with standard ORS.[10]

A number of clinical trials have been performed in children with acute noncholera diarrhea and in children and adults with cholera.[6,14-17] The results of these trials were reviewed in a meeting of experts held in New York on July 18, 2001[18] and summarized in an independent meta-analysis involving 15 studies and 2397 patients.[15] The meta-analysis concluded that, "In children admitted to hospital with dehydration associated with diarrhea, reduced osmolarity rehydration solution is associated with reduced need for unscheduled intravenous infusions, lower stool volume, and less vomiting compared with standard WHO rehydration solution."[15] Similarly, the expert meeting concluded, "For adults with cholera, a reduced osmolarity ORS solution with 75 mmol/L of sodium and 75 mmol/L of glucose is as effective as standard WHO/UNICEF ORS solution."[18] However, some patients with severely purging cholera in an earlier trial that used a solution with 67 mEq/L of sodium did develop asymptomatic hyponatremia[19] and, thus, some concern remained about the possible risk of symptomatic hyponatremia with a 75-mEq/L solution. This concern was not considered sufficient to prevent the use of this solution to treat adults with cholera. It was agreed, however, that the incidence of symptomatic hyponatremia in patients should be monitored when the reduced osmolarity ORS was first introduced for routine use.[18] This conclusion was confirmed in a recently published Cochrane meta-analysis.[20]

Following this recommendation, the International Centre for Diarrhoeal Disease Research Bangladesh (ICDDRB): Centre for Health and Population Research, Dhaka, Bangladesh, decided to (1) introduce the new ORS formulation for routine use at its Dhaka (urban) and Matlab (rural) hospitals for treatment of patients with diarrhea, and (2) to conduct surveillance (phase 4 study) to monitor the occurrence of symptomatic hyponatremia (altered consciousness, seizures, or both associated with biochemical hyponatremia) or other unexpected events while using the new formulation.

METHODS

Study Sites

The study was performed at the Dhaka and Matlab hospitals of ICDDRB: Centre for Health and Population Research over a complete 1-year period (December 1, 2002-November 30, 2003, at the Dhaka hospital and February 2, 2003-January 31, 2004, at the Matlab hospital). Both hospitals have short stay wards in which patients who have diarrhea are admitted for rehydration. The average stay is less than 24 hours. Patients who have diarrhea with complications, such as pneumonia, sepsis, electrolyte abnormalities, severe malnutrition, or seizure or altered consciousness, are admitted to long stay wards for thorough clinical and laboratory assessments and treatment. These patients stay for an average of 5.5 days. Patients with very severe illnesses, such as severe respiratory distress, cyanosis, suspected septic shock, or convulsions, are admitted to the special care wards for more intensive care. The research review and the ethical review committees of the ICDDRB approved the protocol. The patients received standard routine medical care, including the reduced osmolarity ORS; therefore, consent for an experimental protocol was not obtained.

Inclusion and Exclusion Criteria

All patients attending the Dhaka and Matlab hospitals with uncomplicated, acute watery diarrhea who were admitted to the short stay wards and who stayed for at least 8 hours for rehydration were eligible for the study. At the Dhaka hospital, patients with some or severe dehydration attending between 8:30 AM and 8:30 PM and all patients irrespective of their dehydration status attending beyond this time interval are usually admitted to the short stay ward. Patients without any sign of dehydration attending between 8:30 AM and 8:30 PM are referred to a clinic within the ICDDRB premises run by a nongovernment organization. At the Matlab hospital, all patients irrespective of their dehydration status are admitted to the short stay ward.

Dehydration status of the patients was assessed by a senior nurse at the registration desk following the WHO guidelines[21] modified for use in the ICDDRB hospitals. Some dehydration was defined as the presence of at least 2 signs or symptoms (irritable or less active, sunken eyes, dry mucosa, thirst, reduced skin turgor) with at least 1 key sign (irritable or less active, thirst, or reduced skin turgor). Severe dehydration was defined as the presence of signs or symptoms of some dehydration with at least 1 key sign (lethargy or coma, unable to drink but not refusal, or uncountable or absent radial pulse). Patients with complications on admission (lethargy, altered consciousness, convulsion, or other chronic

illnesses) and those patients with associated severe illnesses (pneumonia, sepsis, meningitis, shigellosis, or typhoid fever) that required special care and multiple interventions were excluded from the study.

Procedures

All patients received the new reduced-osmolarity ORS, with the following salt concentrations: sodium, 75 mEq/L; chloride, 65 mEq/L; potassium, 20 mEq/L; and citrate, 290 mg/dL. The solutions for infants aged 6 months or younger used glucose (1351 mg/dL [75 mmol/L]) as the carbohydrate substrate, and the solutions administered to older children and adults used rice powder (40 g/L) as the carbohydrate source in accordance with the standard policy of the ICDDRB. The osmolarity of the glucose solution was 245 mOsm/L, and the osmolarity of the rice ORS was 170 mOsm/L.

Case Detection and Management

Patients who developed seizures or altered consciousness during their hospitalization in the short stay ward were transferred to the long stay ward or the special care ward, where they were clinically assessed and laboratory investigations performed to determine the cause of their symptoms, such as hypoglycemia (blood glucose, <40 mg/dL [<2.2 mmol/L]), hyponatremia (serum sodium, <130 mEq/L), or hypernatremia (serum sodium, >150 mEq/L). In children younger than 2 years, altered consciousness was defined as an abnormally sleepy child who responded to painful stimuli. Altered consciousness among older children and adults was defined as those individuals who were drowsy but who responded to vocal commands.

Protocol for Treatment of Seizure

A standardized protocol was used at both study sites for treatment of patients developing seizures or altered consciousness. Patients were immediately transferred to the long stay or special care wards, an intravenous line was established, and blood glucose was measured from a fingerstick blood sample by using a bedside glucose monitor. Additional venous blood samples were obtained for measurement of serum electrolytes, calcium, and magnesium at the clinical laboratories of the ICDDRB. If a patient was hypoglycemic, he or she was administered intravenous glucose (2.0 mL/kg of 25% glucose). If a patient was not hypoglycemic or if a patient who was hypoglycemic did not respond to the initial glucose infusion, diazepam was slowly administered intravenously to a maximum dose of 0.3 mg/kg. If the seizure persisted, the dose of intravenous diazepam was repeated and phenobarbitone was added (15-20 mg/kg loading dose, followed up with 5 mg/kg per day as maintenance dose in 2 divided doses). After control of the seizure, a spinal tap was performed in patients who were febrile to exclude meningitis, and a venous blood sample was sent for culture to exclude septicemia. A chest radiograph was performed to exclude pneumonia when clinically indicated. Stool cultures for *Shigella, Salmonella,* and *Vibrio* species were performed to look for common bacterial causes of diarrhea, although some patients had received antimicrobial drugs while being treated in the short stay ward because of a clinical diagnosis of cholera or shigellosis. Patients with severe hyponatremia (serum sodium, ≤120 mEq/L) were treated with 3% sodium chloride (12 mL/kg over a 4-hour period) along with restriction of plain water. Follow-up serum sodium estimations were performed if required, according to the patients' response. Patients who were hypernatremic with diarrhea were treated using the study ORS but with provision for water ad lib. Patients suspected of having other infections, including sepsis, were treated with parenteral ampicillin plus gentamicin (infants aged ≤2 months) or ceftriaxone plus gentamicin (patients aged >2 months) for 7 days.

Comparison Group

Because this was not a controlled study, we reviewed the hospital records of all patients admitted to the long stay or special care wards of the Dhaka hospital in the previous year (December 1, 2001-November 30, 2002). Those patients initially admitted to the short stay ward who stayed for at least 8 hours but subsequently developed neurological symptoms (seizure or altered consciousness) and were transferred to the long stay or special care wards were included for comparison.

Data Analysis

All data were collected on case report forms, edited, entered into a personal computer, and analyzed on completion of the study using statistical software (SPSS version 10, SPSS Inc, Chicago, Ill). All episodes of seizure or altered consciousness were identified and recorded, and their association with abnormal levels of serum sodium or glucose was determined. Denominators were the number of children with diarrhea admitted to the short stay wards at the 2 hospitals during the study period, taken from hospital records. The main outcome measure of the study was the incidence of seizures or altered consciousness due to hyponatremia during hospitalization. Hospital records from the Dhaka hospital in the past year were also reviewed to allow comparison of the incidence of symptomatic hyponatremia in the current study period with that of the previous year using χ^2 test. Odds ratio was calculated to estimate the risk of symptomatic hyponatremia using the reduced osmolarity ORS. $P<.05$ was considered statistically significant.

RESULTS

In total, 53 280 patients with diarrhea were monitored at the 2 hospitals (43 700 at the Dhaka hospital and 9580 at the Matlab hospital) during the study period, with 22 536 children aged younger than 60 months. For the comparison period, 48 511 patients were admitted to the short stay ward. Proportionately more male children presented to both hospitals, which might reflect the health-seeking behavior of the Bangladeshi people with a male preference.[22,23] The majority of children

5 years or younger at the Dhaka hospital experienced some dehydration (59%); 12% had severe dehydration and 29% had no sign of dehydration. At the Matlab hospital, 66% of the children of the same age group were admitted with no sign of dehydration (TABLE 1). Among older children and adults, most were admitted with either some dehydration (48% at Dhaka hospital and 53% at Matlab hospital) or severe dehydration (47% at Dhaka hospital and 27% at Matlab hospital). Most children younger than 3 years were brought to the hospital with a history of diarrhea of 2 to 7 days, and most older children (>3 years) and adults attended within 24 hours of the onset of diarrhea (TABLE 2). Younger children had less severe diarrhea, most likely of viral etiology,[24] which would account for the delay in seeking hospital admission.

Twenty-four patients at the Dhaka hospital and 7 at the Matlab hospital developed seizures or altered consciousness during the study, and 54 such patients were identified from Dhaka hospital in the comparison period 1 year earlier (TABLE 3). None of the children older than 3 years or adults treated with the reduced osmolarity ORS developed neurological symptoms associated with hyponatremia. However, during the comparison period, 7 patients older than 3 years developed altered consciousness associated with hyponatremia, of whom 4 were adults. During the study period, 24 children aged 3 years or younger experienced seizures or altered consciousness associated with hyponatremia (21 at the Dhaka hospital and 3 at the Matlab hospital). In the comparison period, 40 patients aged 3 years or younger were identified with symptoms of seizure or altered consciousness associated with hyponatremia.

The overall rate of symptomatic hyponatremia was 0.05% (21/43 700; 95% confidence interval [CI], 0.03%-0.07%) at the Dhaka hospital and 0.03% (3/9580; 95% CI, 0.01%-0.09%) at the Matlab hospital. The overall rate in the comparison period across all age groups was 0.10% (47/48 511; 95% CI, 0.07%-0.13%). Statistical comparison of the incidence rate of symptomatic hyponatremia in the Dhaka hospital between the study vs comparison periods revealed a statistically significant 50% lower incidence of symptomatic hyponatremia in the study period (χ^2=6.80; odds ratio, 0.50; 95% CI, 0.29-0.85; P=.009). Combining the data from the 2 hospitals, the rate was 0.12% (24/20 090; 95% CI, 0.08%-0.18%) for those children aged 3 years or younger; 0.19% (8/4156; 95% CI, 0.10%-0.38%) for those aged 6 months or younger; and 0.10% (16/15 934; 95% CI, 0.06%-0.16%) for those aged 7 to 36 months, following the introduction of the new formulation of ORS. Because patients presenting with severe dehydration are at greatest risk of developing symptomatic hyponatremia while being treated with reduced osmolarity ORS, a subgroup analysis excluding patients with no or some dehydration was performed. The incidence rate during the study period (combined data from Dhaka and Matlab hospitals) was 0.15% (24/16 077; 95% CI, 0.10%-0.22%).

In the 2 hospitals, 7 patients developed seizure or altered consciousness without hyponatremia (Table 3). In 3 patients, symptoms were associated

Table 1. Distribution of Patients by Age, Sex, and Dehydration Status*

	Dhaka Hospital (n = 43 700)						Matlab Hospital (n = 9580)					
		No. (%) of Patients						No. (%) of Patients				
		Sex		Dehydration Status				Sex		Dehydration Status		
Age Groups	Total No. of Patients	Male	Female	None	Some	Severe	Total No. of Patients	Male	Female	None	Some	Severe
≤6 mo	3415	2174 (64)	1241 (36)	1229 (36)	2049 (60)	137 (4)	741	488 (66)	253 (34)	541 (73)	193 (26)	7 (1)
7-36 mo	11 380	7141 (63)	4239 (37)	3463 (30)	6869 (60)	1048 (10)	4554	2927 (64)	1627 (36)	3197 (70)	1233 (27)	124 (3)
37-60 mo	1818	1098 (60)	720 (40)	157 (9)	917 (50)	744 (41)	628	394 (63)	234 (37)	174 (28)	314 (50)	140 (22)
6-15 y	4882	2929 (60)	1953 (40)	293 (6)	2148 (44)	2441 (50)	1211	712 (59)	499 (41)	230 (19)	642 (53)	339 (28)
>15 y	22 205	12 657 (57)	9548 (43)	1110 (5)	10 658 (48)	10 437 (47)	2446	1142 (47)	1304 (53)	490 (20)	1296 (53)	660 (27)

*Some dehydration status is defined as the presence of at least 2 signs or symptoms (irritable or less active, sunken eyes, dry mucosa, thirst, reduced skin turgor) with at least 1 key sign (irritable or less active, thirst, or reduced skin turgor). Severe dehydration status is defined as the presence of signs or symptoms of some dehydration with at least 1 key sign (lethargy or coma, unable to drink but not refusal, or uncountable or absent radial pulse).

Table 2. Duration of Diarrhea Before Admission by Age

	Dhaka Hospital (n = 43 700)				Matlab Hospital (n = 9580)			
		Duration, No. (%), d				Duration, No. (%), d		
Age Groups	Total No. of Patients	≤1	2-7	>7	Total No. of Patients	≤1	2-7	>7
≤6 mo	3415	717 (21)	2391 (70)	307 (9)	741	250 (34)	482 (65)	9 (1)
7-36 mo	11 380	3498 (31)	7253 (64)	629 (5)	4554	2082 (46)	2371 (52)	101 (2)
37-60 mo	1818	989 (54)	798 (44)	31 (2)	628	454 (72)	170 (27)	4 (1)
6-15 y	4882	3027 (62)	1756 (36)	99 (2)	1211	931 (77)	272 (22)	8 (1)
>15 y	22 205	14 210 (64)	7551 (34)	444 (2)	2446	1981 (81)	441 (18)	24 (1)

with hypernatremia. In the comparison period, 7 patients had seizures or altered consciousness without hyponatremia, and 1 of them had borderline hypernatremia (serum sodium, 151.3 mEq/L). One moderately malnourished 8-month-old female died during the study period due to culture-proven shigellosis with severe pneumonia, sepsis, and hyponatremia (serum sodium, 118.5 mEq/L) 3 days after admission.

COMMENT

The results of our large, phase 4 clinical surveillance study demonstrate that the occurrence of symptomatic hyponatremia in older children and adults with diarrhea who are treated with the reduced osmolarity ORS formulation recently recommended by WHO and UNICEF is extremely rare. None of more than 30 000 older children or adults developed symptomatic hyponatremia. Among younger patients (≤3 years), a few developed neurological symptoms associated with hyponatremia while being treated with the new ORS formulation. However, the rate of symptomatic hyponatremia was not higher but rather lower than the rate of symptomatic hyponatremia during the previous year when the older ORS formulation containing a higher amount of sodium was used. Even when patients with diarrhea with no or some dehydration who were less likely to develop symptomatic hyponatremia while being treated with reduced osmolarity ORS were excluded, the incidence rate was still very low.

At these hospitals, fecal specimens are cultured from every 50th patient (a 2% systematic sample) to characterize the etiological agents causing diarrhea. This surveillance demonstrates that approximately 20% of the patients have culture-documented cholera, and the rate has remained reasonably constant over the years. Although fecal cultures were not performed on all the patients in our study, we can assume that cholera was common. In severe cholera, the stool contains high concentrations of sodium; therefore, there was a concern that patients with cholera, especially adults whose stool sodium concentration is much higher than that of children, would be at particularly high risk of hyponatremia when treated with an ORS containing 75 mEq/L of sodium. Although we did not measure serum sodium in our patients, it is reassuring that symptomatic hyponatremia did not occur in older children and adults. Of 21 patients aged 3 years or younger at the Dhaka hospital who had neurological symptoms, 5 (24%) were diagnosed to have

Table 3. Characteristics of Patients Who Developed Seizure or Altered Consciousness While Being Treated With ORS*

	No. of Patients		
	Dhaka Hospital Study Period (n = 24)	Matlab Hospital Study Period (n = 7)	Dhaka Hospital Comparison Period (n = 54)
Age			
≤6 mo	7	4	16
7-36 mo	17	3	31
37-60 mo	0	0	2
6-15 y	0	0	1
>15 y	0	0	4
Sex			
Male	10	4	27
Female	14	3	27
Neurological symptoms			
Seizure	15	5	28
Altered consciousness	9	2	26
Timing of development of symptoms after admission in short stay ward, h			
8-24	8	3	30
25-48	11	2	13
>48	5	2	11
Serum sodium, mEq/L			
<115	4	0	3
115-120	13	0	20
121-125	1	0	20
126-129	3	3	4
130-150	1	3	6
>150	2	1	1
Presentation/clinical diagnoses			
AWD	10	1	21
AWD + pneumonia	7	0	13
AWD + fever	2	4	14
AWD + sepsis	4	2	4
Dysentery + pneumonia + sepsis	1	0	0
AWD + acute renal failure	0	0	1
AWD + hepatic encephalopathy	0	0	1
Bacterial etiology of diarrhea			
Vibrio cholerae	5	1	12
Shigella species	6	1	14
Shigella + nontyphoidal *Salmonella*	1	0	3
Salmonella typhi	0	0	1
Associated findings			
Hypoglycemia	1	1	0
Hypocalcemia	3	0	0

Abbreviations: AWD, acute watery diarrhea; ORS, oral rehydration solution.
*Reduced osmolarity ORS (sodium, 75 mEq/L) was used during the study periods at the Dhaka and Matlab hospitals and the old formulation of ORS (sodium, 90 mEq/L) was used at the Dhaka hospital in the comparison study period. The Dhaka hospital study period was from December 1, 2002, to November 30, 2003; the Matlab hospital study period was from February 2, 2003, to January 31, 2004; and the Dhaka hospital comparison study period was from December 1, 2001, to November 30, 2002.

cholera. Similarly, in the corresponding months of the previous year, 24 (25%) of 47 patients diagnosed with neurological symptoms and hyponatremia had cholera. In a previous trial[19] that used an ORS containing 67 mEq of sodium, moderate hyponatremia (serum sodium, <125 mEq/L) was observed in 8.8% of the patients. An increased number of patients with transient hyponatremia was also reported in another study[16] in which adult patients with cholera were treated with reduced osmolarity ORS containing 75 mEq/L of sodium. However, transient mild hyponatremia, which may also occur with old ORS, should be corrected when a normal diet is resumed. A similar view was expressed by the investigators of ORS trials,[25] although concerns and counter arguments continue.[26] Stool sodium excretion in children with acute watery diarrhea caused by organisms other than *Vibrio cholerae*[27,28] generally does not exceed the concentrations present in the new ORS formulation, and younger children mostly have noncholera diarrhea, and thus these groups are of less concern.

We used rice-based ORS for patients older than 6 months instead of the standard glucose-based ORS recommended by the WHO. Rice-based ORS has been proven to be beneficial in cholera because it is associated with significantly less purging,[29,30] and it is equally effective in diarrhea due to other causes. Because patients treated at our hospitals frequently have cholera, the policy of the ICDDRB hospitals is to use rice-based ORS for children older than 6 months and for adults with diarrhea. The concentrations of the salts (sodium, potassium) and bases are the same in the rice-based and glucose-based formulations and, therefore, we think that the results obtained in our study can be safely extrapolated to glucose-based reduced osmolarity ORS.

Other common causes of seizure or altered consciousness in patients admitted to the special care wards are severe infections, such as shigellosis, salmonellosis, sepsis, meningitis, and severe pneumonia.[31,32] Hypernatremia or hypoglycemia must also be considered in children with diarrhea and seizures, especially in younger children.[33-36] In our study, convulsions due to hypoglycemia were rare, perhaps because of the use of ORS and the early feeding. Benign convulsions in infants and children with mild gastroenteritis due to rotavirus have also been reported.[37,38]

Although this was a 1-year study covering all seasons with a large sample size, there are some limitations. There was no concurrent control for comparison. Although we have compared the results to the previous year's data, there remains the possibility of bias. No phase 4 clinical trial was performed with the older ORS and thus direct comparison was not possible. This was a hospital-based study and may not be representative of the field situation. However, children and adults treated in the community are likely to have milder illness compared with those presenting to a hospital. Therefore, it is likely that hyponatremia will be even less common with the use of reduced osmolarity ORS in the community.

Besides hyponatremia, seizures in patients with diarrhea, especially in younger children, may occur with other associated conditions (hypoglycemia, hypernatremia, hypocalcemia, hypomagnesemia, shigellosis, sepsis, pneumonia, meningitis, high fever), and it is difficult to determine the actual cause of seizure when 2 or 3 conditions overlap. In addition to hyponatremia, 7 children developing seizures in our study had other conditions: 1 had shigellosis with clinical sepsis and pneumonia, 1 had shigellosis and pneumonia, 1 had shigellosis and hypoglycemia, 1 had pneumonia and hypocalcemia, 2 had pneumonia and clinical sepsis, and 1 had hypocalcemia. All were categorized as having seizures from hyponatremia rather than the other conditions, and all presented with watery diarrhea. Younger children who experienced enteric infection with *Shigella* species other than *S dysenteriae type 1* often present with watery diarrhea,[39] which delays antimicrobial treatment and the benefits of early specific therapy.

Based on the experience from our study and other trials,[31,32,37,38,40,41] we conclude that diarrheal diseases are most often uncomplicated and simple to treat but a few patients may still present with or develop complications during treatment, irrespective of fluid therapy and whether it is iso-osmolar or hypo-osmolar. Therefore, centers treating infectious diarrheal diseases should be vigilant about the development of such complications and should follow a protocolized treatment strategy to handle them. The formulation of reduced osmolarity ORS recently recommended by WHO and UNICEF is safe and can be used in the treatment of all patients with diarrhea, irrespective of their age and the cause of diarrhea.

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