Introduction of a New Hypo-osmolar Oral Rehydration Solution to Routine Use in the Treatment of Diarrhoeal Disease: A Phase IV Clinical Trial

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ABSTRACT

Background: In May 2002, following the recommendations made at a meeting of experts held in New York in July 2001, WHO and UNICEF recommended the use of a new, low sodium, low glucose, low osmolarity oral rehydration salts (ORS) solution in place of the previous formulation for use in the treatment and prevention of dehydration due to diarrhoea in all age groups and for all causes. Although the safety data in patients with cholera, while limited, was reassuring, it was recommended that the safety of this new formulation be monitored in a post-marketing surveillance study, measuring the incidence of symptomatic (seizure/altered consciousness) hyponatraemia (serum sodium <130 mmol/L) during treatment with the new formulation of ORS.

Objective: To measure the incidence of symptomatic hyponatraemia (seizure/altered consciousness) during treatment of diarrhoea with the newly recommended ORS formulation.

Methods: The study was conducted at the ICDDR, B hospitals in Dhaka and in Matlab over a complete year (from December, 2002 to November 2003 in Dhaka hospital and from February, 2003 to January 2004 in Matlab hospital). In the two hospitals, a total of 53,280 patients were admitted to the rehydration ward with uncomplicated watery diarrhoea to be treated with the new ORS solution for at least for 8 hours. Patients with associated severe illnesses, or patients directly admitted to the special care unit of the hospitals were excluded from the study. During treatment in the rehydration ward, patients developing symptoms (seizure/altered consciousness) were immediately transferred to the special care unit for treatment and clinical and laboratory investigations to identify the cause of the symptoms. Patients' records were analysed to find out if the symptoms were associated with hyponatraemia, and if the development of hyponatraemia was due to intake of the new ORS. As this study was not a controlled clinical trial, we reviewed also the records of the Dhaka hospital for the corresponding previous year (from December, 2001 to November, 2002) to compare our findings with the situation when the old ORS formulation was the only ORS solution in use.

Results: In both hospitals, a total of 53,280 patients were monitored (22,536 were less than 60 months old, 6,093 were 6 to 15 years of age, and 24,651 were more than 15 years old). In patients less than 60 months of age, on admission 51% had signs of some dehydration and 10% signs of severe dehydration. In patients 6 to 15 years old, 46% had signs of some dehydration and 46% had signs of severe dehydration. Finally, among patients older than 15 years of age, 48% had signs of some dehydration, while 45% had signs of severe dehydration. No single adult patient experienced any symptoms (seizure/altered consciousness) associated with hyponatraemia. A total of 31 patients less than 60 months of age experienced seizure/altered consciousness during treatment with the new ORS formulation. Among those, 24 presented symptoms (seizure/altered consciousness) associated with hyponatraemia (serum sodium <130 mmol/L). Overall the incidence rate of symptomatic hyponatraemia was 0.05% per year in the Dhaka hospital, and 0.03% per year in the Matlab hospital. The review of the hospital records from the Dhaka hospital showed that the incidence rate of symptomatic hyponatraemia was 0.09% per year (47 cases of symptomatic hyponatremia) for the year prior to the initiation of this study.

Conclusion: Concerns about the safety of the new reduced osmolarity ORS centers on its use in patients with cholera especially adults. As no single adult diarrhoea patients experienced symptoms (seizure/altered consciousness) associated with hyponatraemia, this finding should

be reassuring for the clinicians, policy makers and producers of ORS. In addition, the results of this study demonstrates that the occurrence of seizure/altered consciousness associated with hyponatraemia in patients treated with the new ORS formulation is rare and that the incidence rate of symptomatic hyponatremia associated to the use of the new ORS is less than the incidence rate observed with the old ORS formulation. Based on the results of this study, we can conclude that the new reduced osmolarity oral rehydration salts solution recommended by WHO and UNICEF is safe and that it can be used for the treatment of acute diarrhoea of all etiologies and in all age groups.

INTRODUCTION

Since 1978, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) have recommended the use of a single formulation (Na 90 mmol/L, K 20 mmol/L, Cl 98 mmol/L, Citrate 10 mmol/L glucose 111 mmol/L and osmolarity 311 mosmol/L) of oral rehydration salts (ORS) solution for prevention and treatment of dehydration from diarrhoeal diseases due to any aetiology, including cholera, irrespective of patients' age[1]. The use of this ORS (WHO-ORS) has contributed to the dramatic global reduction in deaths from diarrhoeal diseases over the period[2]. The main limitation of this ORS, however, is that it does neither reduce stool volume nor diarrhoea duration[3], two factors that are considered important for its acceptance by mothers and health workers, who would like to see early resolution of diarrhoea. There has also been concern that the solution, which is slightly hyperosmolar relative to plasma, might induce development of hypernatraemia or an osmotically driven increase in the 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 sodium with a total osmolarity of 250 mosmol/l[7].

Recent efforts to improve the efficacy of ORS have focused particularly on solutions of reduced osmolarity (e.g., ranges of Na = 60-75 mmol/L, and of glucose = 75-90 mmol/L)[8]. These solutions generally preserve the 1:1 molar ratio of sodium to glucose that is crucial for efficient co-transport of sodium, but presents a lower osmolar load to the intestinal tract than does WHO-ORS. Animal[9] and human studies[10] indicate that such solutions might be better designed for optimal water and electrolyte transport into blood stream. In these intestinal perfusion studies[7,10], solutions of reduced-osmolarity have been demonstrated to improve net water absorption and equivalent net sodium absorption compared with standard WHO-ORS[10]. A number of clinical trials were performed in children with acute non-cholera diarrhoea and in children and adults with cholera diarrhoea[11-15]. The results of these trials were reviewed in a meeting of experts held in New York in July 2001[16] and in two independent meta-analyses. The meta-analysis performed on the 15 studies evaluating the efficacy of the low osmolarity ORS solution in children, involving 2397 randomized patients[13], concluded that "In children admitted to hospital with dehydration associated with diarrhoea, 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." However, the review of the studies conducted in adults with cholera, performed during the New York meeting mentioned above[16], concluded "For adults with cholera, a reduced osmolarity ORS solution with 75 mEq/l of sodium and 75 mmol/l of glucose is as effective as standard WHO/UNICEF ORS solution. Nevertheless, some concern remained about the possible risk of symptomatic hyponatraemia with this solution. This concern is not considered sufficient to prevent the use of this solution to treat adults with cholera. It was agreed, however, that, to gain additional clinical data on the safety of reduced osmolarity ORS, the incidence of biochemical and symptomatic hyponatraemia should be monitored when this solution is first introduced for routine use." This conclusion has been confirmed in a recently published Cochrane meta-analysis [17]

Based on the conclusion of the New York meeting of experts, and because of the improved effectiveness of reduced osmolarity ORS solution, especially for children with acute, non-cholera diarrhoea, the WHO and the UNICEF decided in May 2002 to recommend that countries use and manufacture a low sodium, low glucose, low osmolarity ORS formulation (Na 75 mmol/l, K 20 mmol/l, Cl 65 mmol/l, citrate 10 mmol/l, glucose 75 mmol/l) in place of the previously recommended ORS solution that had a total osmolarity of 311 mOsm/l.

It was emphasized that this reduced osmolarity ORS may be used in place of standard ORS for treatment of adults with cholera, but further monitoring was required to better assess the risk, if any, of symptomatic hyponatraemia.

Following this recommendation, the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDRB: Centre for Health and Population Research), Dhaka, Bangladesh decided to introduce the new ORS formulation for routine use at its Dhaka (urban) and Matlab (rural) hospitals for treatment of diarrhoeal patients, and to conduct a Phase IV (post marketing, surveillance study) clinical trial to monitor the occurrence of symptomatic hyponatraemia (altered consciousness and/or seizures associated with biochemical hyponatremia) or any other unexpected events while using the new formulation.

METHODS

Study site - The study was conducted at the Dhaka and Matlab hospitals of ICDDRB: Centre for Health and Population Research over a complete one-year period (December 2002 to November 2003 at the Dhaka hospital, and February 2003 to January 2004 at Matlab hospital). Research Review and the Ethics Review Committees of the Centre approved the protocol.

Sample size - Based on the average yearly patient visits, 60,000 patients were estimated to be monitored (symptom based monitoring- development of seizure/altered consciousness) at the Dhaka hospital and, 15,000 at the Matlab hospital during one-year study period.

All patients attending the Dhaka and Matlab hospitals with uncomplicated, acute watery diarrhoea, and admitted to the Short Stay Ward >8 hours (arbitrarily) for rehydration were eligible for this study.

Patients with complications on admission (lethargy, altered consciousness and other chronic illnesses) and those with associated severe illnesses (e.g. pneumonia, sepsis, meningitis, shigellosis and typhoid fever) that required special care and multiple interventions were excluded from the study.

Procedures - All infants aged 6 months and less received the new (low sodium, low osmolarity) glucose-based ORS (Na: 75, Cl: 65, K: 20, citrate:10, glucose: 75 mmol/L, and osmolarity: 245 mosmol/L), and patients aged older than 6 months including adults received a low sodium rice-based ORS (Na: 75, Cl: 65, K: 20, citrate: 10 mmol/L, and rice powder, 40 g/L with in vitro osmolarity 170 mosmol/L) in accordance with the standard policy of the Centre.

Surveillance and case management - Patients who developed seizure or altered consciousness during their hospitalization in the Short Stay Ward were transferred to the inpatient ward (Special Care Unit), where they were clinically assessed, and where laboratory investigations were performed to determine if their symptoms were associated with hyponatraemia (defined as serum sodium level below 130 mEq/L) or if they were attributable to other causes.

Protocol for management of seizure - Although rare during rehydration therapy of acute watery diarrhoea, seizure is an important and serious adverse events, often associated with

metabolic abnormalities such as hypoglycaemia, and/or electrolyte abnormalities, particularly hyponatraemia, and hypernatraemia. A standardized protocol was used at both study sites for management of seizures:

- Patients developing seizure/altered consciousness were immediately transferred to the Special Care Unit, an intravenous line was established, and blood glucose was measured from finger blood samples using bedside glucose monitoring machine. Additional blood samples were obtained for estimation of serum electrolytes, calcium, and magnesium at the clinical laboratories of the Centre.
- If a patient was found hypoglycemic (blood glucose <2.2 mmol/L), s(he) was given intravenous glucose (2.0 ml/kg of 25% glucose).
- If a patient was not hypoglycemic and also when a hypoglycemic patient did not respond to initial glucose infusion, diazepam was slowly administered through intravenous route in a dose of maximum 0.3 mg/kg. If the seizure persisted, the dose of intravenous diazepam was repeated and additionally phenobarbitone was instituted parentally (15 - 20 mg/kg loading dose, followed by 5 mg/kg per day as maintenance dose in 2 divided doses).
- After control of seizure, a lumber tap was performed in febrile patients to rule out meningitis.
- A venous blood sample was also sent for culture to exclude septicemia.
- Chest X-ray was performed to exclude pneumonia, when clinically indicated.
- Patients with a serum sodium of =120 mmol/l were treated with 3% NaCl (12 ml/kg over a 4-hour period) along with restriction of plain water.
- Hypernatraemic (serum sodium >150 mmol/L) patients with diarrhoea were managed using the study ORS but with provision for water *ad lib*.

Patients suspected to have other infections, including sepsis, were treated with parenteral ampicillin plus gentamicin (infants aged 2 months or younger), or ceftriaxone plus gentamicin (patients older than 2 months) for 7 days.

Data analysis - All relevant data were collected on pre-designed Case Report Forms (CRFs), edited, entered onto a personal computer, and were analysed upon completion of the study using statistical software (SPSS PC+, version 10). The main outcome measure of the study, at both sites, was the occurrence of seizures or altered consciousness during hospitalization. All episodes of seizure/altered consciousness were identified and recorded, and their eventual association with abnormal levels of serum sodium or glucose was determined. In addition, the rate of hyponatraemia and hypernatraemia, and other important events were also evaluated by examining the clinical history and the results of the laboratory investigations. Hospital records of the immediate past year were also reviewed to determine the evolution of the incidence of symptomatic hyponatraemia between the current study period and the previous year.

RESULTS

A total of 53,280 patients with diarrhoea were monitored at the two hospitals (43,700 at Dhaka hospital and 9,580 at Matlab hospital) during the study period. The distribution of

patients per age group and per hospital is presented on Table 1. The degree of dehydration on admission of the patients included in this study is shown on Table 2. The majority of children below 5 years of age presented with some dehydration (51%) and a few presented with severe dehydration (10%). Among older children and adults, almost all presented with either some dehydration (48%) or severe dehydration (45%).

Children aged less than 5 years consulted at the hospitals in their majority after 2 to 7 days of diarrhoea, while older children and adults consulted after less than one day of diarrhoea (Table 3).

None of the older children and adults treated with the new ORS formulation developed neurological symptoms (seizure/altered consciousness) associated with hyponatraemia, and only 24 younger children (<3 years) experienced seizure/altered consciousness associated with hyponatraemia in both hospitals (21 at the Dhaka hospital and 3 at the Matlab hospital) (Table 4). This represents an overall incidence rate for symptomatic hyponatraemia of 0.05% per year at the Dhaka hospital and 0.03% per year at the Matlab hospital, following the introduction of new formulation of ORS solution. The aetiological diagnoses or associated illnesses identified in these symptomatic cases are detailed in Table 4. It should be noted also that in the two hospitals, 7 patients developed seizure/altered consciousness without hyponatraemia (Table 4). In two of them, these symptoms were associated with hypernatremia.

Since this was not a controlled study, we reviewed the hospital records of the Dhaka hospital for the previous years (December 2001 to November 2002). During the comparison period, 47 patients were identified with symptomatic (seizure/altered consciousness) hyponatraemia, for an overall incidence rate of 0.09% per year (Table 5). During that same period, 7 patients had seizure/altered consciousness not associated with hyponatremia, and in one of them, these symptoms were associated with hypernatremia. (Table 5).

DISCUSSION

The results of this large, phase IV clinical trial demonstrate that the occurrence of symptomatic (seizure/altered consciousness) hyponatraemia in older children and adult patients with diarrhoea, treated with the new ORS formulation recently recommended by WHO and UNICEF is extremely rare, as we could not identify one case in more than 30,000 patients treated. Although stool culture was not performed on admission, the data of the Diarrhoeal Disease Surveillance system (2% systematic sample of all patients attending the Dhaka hospital and all patients attending the Matlab hospital of ICDDR,B) (Faruque ASG, personal communication), indicates that about 10% of adult patients admitted to Short Stay Wards are expected to have cholera.

It should be noted that, in this study, we used rice-based ORS for patients aged more than 6 month, instead of the standard glucose-based ORS recommended by WHO. The reason for using rice-based ORS in this study were as follows: a) rice-based ORS has been proven to be beneficial in cholera;[18,19] b) Dhaka and Matlab hospitals are in cholera endemic area; c) the policy of the ICDDRB is to use rice-based ORS for children more than 6 months and for adults with diarrhoea. However, the concentrations of the salts (sodium, potassium) and bases are the same in the rice- and glucose-based formulations and therefore, we feel that the results obtained in this study can be safely extrapolated to glucose-based low osmolarity ORS.

Among the younger patients, a few of them did develop neurological symptoms (seizure/altered consciousness) as well as hyponatraemia while treated with the new ORS formulation. However, whether these children developed hyponatraemia because of the new ORS or because of some other reason could not be determined in the absence of performing baseline serum sodium estimation, and without strictly measuring intake (ORS, and water) and output (stool). Despite this limitation, the incidence rate of symptomatic hyponatraemia was found to be very low (0.05% per year in Dhaka and 0.03% per year in Matlab hospital), rates lower than the rate observed during the corresponding months of the previous years when the standard WHO-ORS was routinely used.

From the patho-physiological point of view, stool sodium excretion in children with acute watery diarrhoea, except cholera,[20, 21] do not exceed the amount present in the new ORS formulation. In this large study, out of 21 patients who had neurological symptoms, 4 (19%) were diagnosed to have cholera. Similarly, in the corresponding months of the previous year, 23% of the patients diagnosed with symptomatic hyponatraemia had cholera (11 out of 47). From our experience of treating a large number of diarrhoeal patients each year (approximately 100,000/ year), we observed that development of hyponatraemia and hypernatraemia is rare when ORS is prepared appropriately and administered in correct amounts. Usually, the risk of developing symptomatic hyponatraemia is increased when dehydrated children are inappropriately managed (e.g. offering too much plain water). Other common causes of seizure/altered consciousness associated with hyponatraemia in patients admitted to the special care unit of ICDDRB hospital are severe infections such as shigellosis, salmonellosis, sepsis, meningitis, and severe pneumonia.[22, 23] Some of the children who developed neurological symptoms and hyponatraemia in this study also had such infections.

Concerns expressed about the safety of reduced-osmolarity ORS during the expert meeting held in New York in July 2001, was mostly for the management of patients with cholera, particularly adults. As we did not observe neurological symptoms associated with hyponatraemia in any of our adult patients, our findings should reassure the clinicians as well as the policy makers, and the producers of ORS with regards to the safety of this new formulation.

Based on the results of this study, we consider it reasonable to conclude that the formulation of reduced-osmolarity oral rehydration salts solution, recently recommended by WHO and UNICEF, is safe and can be used in the management of all diarrhoeal patients, irrespective of their age and the aetiology of diarrhoea.

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Table 1. Distribution of patients admitted in the two hospitals per age groups

Age Groups	Dhaka hospital	Matlab hospital	Total
=6 months	3,415	741	4,156
7 - 60 months	13,198	5,182	18,380
6 - 15 years	4,882	1,211	6,093
> 15 years	22,205	2,446	24,654
Total	43,700	9,580	53,280

Table 2. Dehydration status of patients per age groups on admission

Age groups	Dehydration status (%)					
	No sign		Some		Severe	
	c	%	n	%	n	%
= 6 months	1770	(0.43)	2242	(0.54)	144	(0.03)
7 - 60 months	6931	(0.38)	9342	(0.51)	2107	(0.11)
6 -15 years	523	(0.08)	2790	(0.46)	2780	(0.46)
>15 years	1599	(0.07)	11,955	(0.48)	11,097	(0.45)

Table 3. Baseline characteristics

Age groups	Duration of diarrhoea before admission		
	< 1day (%)	2 - 7 days (%)	> 7 days (%)
=6 months	24	69	7
7 - 60 months	38	58	4
6 - 15 years	65	33	2
> 15 years	66	33	1

Table 4. Summary information of cases who developed seizure and/or altered consciousness while treated with low osmolarity ORS.

Seizure/altered consciousness with hyponatremia	No. of cases Dhaka Hospital	No. of cases Matlab Hospital
Cholera alone	4	
Cholera + Severe Pneumonia	1	
Shigellosis alone	1	
Shigellosis + hypoglycemia	1	1
Shigellosis + Pneumonia	3	
AWD + severe pneumonia	2	
AWD + pneumonia + hypocalcaemia	1	
AWD + Hypocalcaemia	2	
AWD alone	5	
Shigellosis + salmonellosis	1	
AWD + fever		1
Seizure/altered consciousness without hyponatremia		
AWD + pneumonia	1	
AWD + pneumonia + hypernatraemia	1	
AWD + pneumonia + hypocalcaemia	1	
AWD + meningitis		1
AWD + clinical sepsis + hypernatremia		1
Shigellosis alone		1
Cholera alone		1

AWD= acute watery diarrhoea

Table 5. Summary information of cases who developed seizure and/or altered consciousness while treated with the old ORS formulation (standard ORS) at the Dhaka hospital

Seizure/altered consciousness with hyponatremia	No of cases
Shigellosis	8
AWD + Severe pneumonia	5
AWD + Acute renal failure	1
AWD + Bronchial asthma	1
Cholera alone	6
Hepatic encephalopathy + Cholera	1
Shigellosis + Salmonellosis	2
Shigellosis + Cholera	1
Cholera + Pneumonia	3
Shigellosis + Pneumonia	2
Shigellosis + Salmonellosis + Pneumonia	1
Typhoid fever	1
AWD alone	15
Seizure/altered consciousness without hyponatraemia	
AWD + meningoencephalitis	1
AWD + bronchopneumonia	1
AWD + Sepsis	1
AWD + febrile convulsion	1
AWD + hypernatraemia	1
AWD alone	1
Cholera alone	1