

REDUCED OSMOLARITY ORAL REHYDRATION SALTS (ORS) FORMULATION



A REPORT FROM A MEETING OF EXPERTS

JOINTLY ORGANISED BY UNICEF AND WHO

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CHILD AND ADOLESCENT HEALTH AND DEVELOPMENT
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Background

For more than 25 years WHO and UNICEF have recommended a single formulation of glucose-based Oral Rehydration Salts (ORS) to treat or prevent dehydration from diarrhoea of any aetiology, including cholera, and in individuals of any age (1).

This product, which makes a solution that contains 90 mEq/l of sodium with a total osmolality of 311 mOsm/l (Table 1), has been used worldwide and has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease during this period (2). It has been well established, however, that ORS solution does not reduce stool output or duration of diarrhoea (3). There has been concern that this may limit its

sodium and have a total osmolality of 250 mOsm/l (7).

During the past 20 years, numerous studies have been undertaken to develop an "improved" ORS that would be optimally safe and effective for treating or preventing dehydration in all types of diarrhoea, and would also cause reduced stool output or have other clinical benefits when compared with standard ORS. Two approaches have been used: (i) modifying the amount and type of organic carrier(s) used in ORS to promote intestinal absorption of salt and water (this has included replacing glucose with complex carbohydrates, i.e. maltodextrins or cooked rice powder, or certain amino acids, or combining an amino acid with glucose), and (ii) reducing the osmolality of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption (this was done either by replacing glucose with a complex carbohydrate or by reducing the concentration of glucose and salt in the solution).

At a previous meeting in Dhaka, Bangladesh, in 1994 (8), studies that evaluated these two approaches were reviewed. Conclusions reached at that meeting were:

- None of the tested formulations containing an amino acid or maltodextrin was considered sufficiently effective or practical to replace standard ORS (9),
- Rice-based ORS significantly reduces stool output and duration of diarrhoea when compared to standard ORS for adults and children with cholera, and may be used to treat such patients wherever its preparation is convenient (10), and
- Rice-based ORS is not superior to standard glucose-based ORS in the treatment of children with acute non-cholera diarrhoea, especially when food is given shortly after rehydration, as is recommended to prevent malnutrition (10-12).

Concerning ORS formulations in which osmolality was reduced by lowering the content of

Table 1

Composition of standard and reduced osmolality ORS solutions¹

	Standard ORS solution (mEq or mmol/l)	Reduced Osmolality ORS solutions		
		(mEq or mmol/l) (21)	(mEq or mmol/l) (6, 14, 22-27)	(mEq or mmol/l) (13, 15-18, 28-29)
Glucose	111	111	75 - 90	75
Sodium	90	50	60 - 70	75
Chloride	80	40	60 - 70	65
Potassium	20	20	20	20
Citrate	10	30*	10	10
Osmolality	311	251	210 - 260	245

* 30 mmol/l of bicarbonate instead of 10 mmol/l of citrate

¹ Other reduced osmolality ORS formulations include ORS in which glucose was replaced by maltodextrin (20) or sucrose (24).

acceptance by mothers and health workers, who want a treatment that causes diarrhoea to stop. There has also been concern that the solution, which is slightly hyperosmolar when compared with plasma, may risk, hyponatraemia or an osmotically driven increase in stool output, especially in infants and young children (4-6). For this reason paediatricians in some developed countries recommend that ORS contain about 60 mEq/l

glucose and salt to 75-90 mmol/l and 60-75 mEq/l respectively (total osmolarity of 225-245 mOsm/l) (Table 1), it was concluded that:

- Reduced osmolarity ORS significantly reduces stool output and duration of diarrhoea when compared to treatment with standard ORS for children with acute non-cholera diarrhoea, but there were insufficient data to reach firm conclusions with regard to the possible risks and benefits of reduced osmolarity ORS for treatment of patients with cholera, especially adults. Moreover, the compositions of the reduced osmolarity ORS solutions differed with regard to concentrations of sodium and glucose, and in total osmolarity, and it was not possible to recommend one formulation as being superior to the others.

It was recommended that additional studies be done in adults with cholera and in children with acute non-cholera diarrhoea comparing standard ORS to a single reduced osmolarity ORS solution containing 75

mmol/l of glucose and 75 mEq/l of sodium, and a total osmolarity of 245 mOsm/l (Table 1). This formula was selected to provide a sodium concentration only modestly less than that in standard ORS, which was considered important for treatment of adults with cholera in whom sodium losses are greatest, and to provide glucose in a molar concentration equal to that of sodium, which is essential to facilitate sodium absorption. These studies were conducted from 1995 to 1998 in six countries (Bangladesh, Brazil, India, Indonesia, Peru and Viet Nam), and were supported by the Department of Child and Adolescent Health and Development of WHO (Geneva), the Applied Research of Child Health (ARCH) project (Boston, USA), USAID and UNICEF. The objectives of the present meeting were to review the results of both the previous and the new studies, and to provide technical recommendations to WHO and UNICEF on the safety and efficacy of reduced osmolarity ORS in adults and children with cholera, and in children with acute non-cholera diarrhoea.

Reduced osmolarity ORS in adults with cholera

Trial of 75 mEq sodium, 75 mmol glucose ORS

Results of a recent study by Alam et al comparing the efficacy and safety of reduced osmolarity ORS (RED OSM ORS) and standard ORS (WHO ORS) in adults with cholera (13) were reviewed. The study enrolled 300 patients who presented with signs of severe dehydration (147 treated with reduced osmolarity ORS and 153 treated with standard ORS). There were no differences in: stool output during the first 24 hours, total stool output, duration of diarrhoea, need for unscheduled IV therapy, or the incidence of treatment failure when comparing patients given reduced osmolarity ORS with those receiving standard ORS.

Patients who received reduced osmolarity ORS did have an increased risk of hyponatraemia after 24 hours of treatment, defined as a serum sodium concentration <130 mEq/l (29 patients treated with reduced osmolarity ORS developed hyponatraemia versus only 16 in the group treated with standard ORS; OR=2.1, 95% CI 1.1 to 4.1). However, the proportion of patients with serum sodium < 125 mEq/l 24 hours after initiation of treatment was similar in the two groups. No patient had symptoms due to hyponatraemia.

Additional data, not included in the published report, were also reported. Among 35 patients who underwent sodium balance studies, mean sodium balance was negative in both groups and the negative balance was

Table 2

Comparison of serum sodium values at 24 hours in adult cholera patients treated with reduced osmolarity ORS or standard ORS².

Author	No. analysed: WHO ORS/RED. OSM ORS	Osmolarity of RED. OSM ORS (mOsm/l)	Serum sodium at 24 hours		Study weight in pooled analysis (10)
			Mean sodium with WHO ORS: mEq/l (sd)	Mean reduction in sodium with RED. OSM ORS: mEq/l (se2)	
Faruque et al. (14)	29/34	249	137 (4.4)	2.4 (1.8)	0.128
Pulungsih et al. (15)	67/64	245	141 (9.9)	0.7 (2.2)	0.105
Alam et al.(13)	153/147	245	135 (4.3)	1.2 (0.3)	0.767

se2 = variance of the mean

sd = standard deviation

Pooled analysis:

- Estimated mean serum Na at 24 hours for patients given standard WHO ORS: 136 mEq/l
- Mean reduction in serum sodium for patients given reduced osmolarity ORS solutions: 1.3 mEq/l; 95% CI: 0.3 to 2.3

The studies by Alam (13) and Pulungsih (15) tested reduced osmolarity ORS formulations containing 75 mEq/l of sodium and 75 mmol/l of glucose, for a total osmolarity of 245 mOsm/l. The study by Faruque (14) tested a reduced osmolarity ORS formulation containing 67 mEq/l of sodium and 89 mmol/l of glucose, for a total osmolarity of 249 mOsm/l.

greater in the reduced osmolarity ORS group. However, there was wide variability in balance outcomes and this difference did not achieve statistical significance.

Combined analysis with earlier trials

Results of this study were analysed together with those of two earlier studies (14–15) that compared the efficacy and safety of reduced osmolarity ORS to that of standard ORS in adults with cholera. The combined analysis showed a minimal, and statistically insignificant, mean reduction of 0.5 ml/kg (95% CI: -14.6 to +15.6) in stool output during the first 24 hours among patients given reduced osmolarity ORS when compared to those receiving standard ORS. A small, but statistically significant reduction in mean serum sodium of 1.3 mEq/l (95% CI: 0.3 to 2.3) was observed at 24-hours in patients treated with reduced osmolarity ORS when compared to those given standard ORS (Table 2). In these

studies no patient who developed hyponatraemia became symptomatic.

Conclusions

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 was 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. Because seizures are rare in adults with cholera, an increase in the incidence of this symptom should be easily recognised.

Reduced osmolarity ORS in children

Children with acute non-cholera diarrhoea

Meta-analysis of all studies

A recently published meta-analysis of trials of reduced osmolarity ORS (19) was reviewed. The meta-analysis included all randomized trials in which a reduced osmolarity ORS containing glucose, maltodextrin or sucrose was used (total osmolarity 210 - 268 mOsm/l). The inclusion of a single study of an ORS containing maltodextrin instead of glucose, but with a sodium concentration of 90 mEq/l, was questioned because of clinical evidence that maltodextrin ORS does not act as a reduced osmolarity ORS (20). However, exclusion of this study from the meta-analysis did not change its conclusions. All other studies included in the meta-analysis had sodium concentrations ranging from 50 to 75 mEq/l.

Table 3 shows the results of the meta-analysis, which were as follows: (i) Use of a reduced

osmolarity ORS was associated with a significant reduction (about 35%) in the need for unscheduled IV fluids. The need for unscheduled IV therapy is defined as the clinical requirement for intravenous infusion after oral rehydration has been started. This outcome is based on clinical judgement that oral treatment has failed either to correct dehydration or to maintain hydration. In many peripheral treatment sites, where IV therapy is often unavailable, reducing the need for unscheduled IV therapy would reduce the risk of death from dehydration. (ii) In each of the 11 studies, except the one using maltodextrin, there was a trend toward reduced stool output in patients given reduced osmolarity ORS and in the pooled analysis this reduction (about 20%) was statistically significant. (iii) There was a significant reduction (about 30%) in the incidence of vomiting in children given reduced osmolarity ORS. And (iv) the incidence of hyponatraemia (serum sodium <130 mEq/l at 24 hours) was greater among children given reduced osmolarity ORS. This difference was not statistically significant (51 children treated with reduced osmolarity ORS developed hyponatraemia versus 36 children treated with standard ORS; OR=1.45. 95% CI 0.93 to 2.26), but could be as much as twice that associated with standard ORS.

Table 3

Summary of the results of the published meta-analysis of all randomized clinical trials comparing reduced osmolarity ORS with standard ORS in children with acute non-cholera diarrhoea (19)

	Pooled standardized mean difference (log scale) in children receiving RED. OSM ORS when compared to those receiving WHO ORS (95% CI)	Odds ratio for children receiving RED. OSM ORS when compared to those receiving WHO ORS: (95% CI)
Unscheduled IV therapy	-	0.61 (0.47 - 0.81)*
Stool output	-0.214 (-0.305 to -0.123)*	-
Vomiting	-	0.71 (0.55 - 0.92)*
Hyponatraemia	-	1.45 (0.93 - 2.26)

* p<0.05

Multicentre trial of 75 mEq sodium, 75 mmol glucose ORS

Results of the recent multicentre study evaluating the efficacy and safety of reduced osmolarity ORS among children (16) were then reviewed separately. This study is included in the meta-analysis described above. It was conducted in 5 countries and enrolled 675 children aged 1-24 months (341 received reduced osmolarity ORS and 334 received standard ORS). In contrast to the meta-analysis summarized above, this study did not show any difference in stool output or vomiting between the two treatment groups. There was, however, as in earlier studies, a significant reduction of about 33%

in the use of unscheduled IV fluids in those who received reduced osmolarity ORS (34 children treated with reduced osmolarity ORS required unscheduled IV therapy versus 50 children in the group treated with standard ORS; OR=0.6, 95% CI 0.4 to 1.0). The incidence of hyponatraemia (serum sodium <130 mEq/l) was 11% in the reduced osmolarity ORS group and 9% in the standard ORS group (37 children treated with reduced osmolarity ORS developed hyponatraemia versus 29 in the group treated with standard ORS; OR=1.3, 95% CI 0.8 to 2.2.).

Re-analysis of ORS efficacy stratified for sodium content

A re-analysis of all studies was conducted, stratifying them according to the sodium content of the reduced osmolarity ORS: (i) reduced osmolarity ORS containing less than 75 mEq/l of sodium (range 60 to 70 mEq/l), and (ii) reduced osmolarity ORS containing exactly 75 mEq/l of sodium. Results of this re-analysis are presented in Table 4. These show that ORS solution with a sodium concentration of 75 mEq/l and ORS solution with a sodium concentration of less than 75 mEq/l are more effective than standard ORS with regard to need for unscheduled IV therapy and occurrence of vomiting, and that the incidence of hyponatraemia, while not significantly higher than for standard ORS, could be up to double its incidence. Test for interaction could not differentiate between the efficacy of ORS solutions containing less than 75 mEq/l of sodium and that of ORS solution containing 75 mEq/l of sodium, even on unidirectional tests of significance.

Children with cholera

Multicentre trial of 75 mEq sodium, 75 mmol glucose ORS

A small subgroup of patients enrolled in the multicentre study (9%) had culture-proven cholera. The safety and efficacy of reduced

osmolarity ORS in those children was considered. The need for unscheduled IV fluids, although higher than in children with non-cholera diarrhoea, was lower in children treated with reduced osmolarity ORS than in the children receiving standard ORS (30% in children treated with reduced osmolarity ORS vs. 44% in children treated with standard WHO ORS). Although mean serum sodium in

Table 4

Pooled analysis stratified according to the sodium content of the reduced osmolarity ORS

	RED. OSM ORS with < 75 mEq/l of sodium	RED. OSM ORS with 75 mEq/l of sodium
Odds ratio for unscheduled IV therapy for patients given RED OSM ORS when compared to those given WHO ORS	N= 4 studies N=678 children 0.65 (0.41 to 1.00)	N=4 studies N=1175 children 0.56 (0.39 to 0.80)*
Pooled standardized mean difference in the log scale for stool output in children given RED OSM ORS when compared to those given WHO ORS	N=8 studies N=771 children -0.37 (-0.72 to -0.02)*	N=4 studies N=1049 children -0.13 (-0.34 to 0.06)
Odds ratio for vomiting for patients given RED OSM ORS when compared to those given WHO ORS	N=3 studies N=270 children 0.49 (0.27 to 0.91)*	N=3 studies N=1031 children 0.74 (0.58 to 0.95)*
Odds ratio for hyponatraemia (<130 mEq/l) for patients given RED OSM ORS when compared to those given WHO ORS	N=3 studies N=139 children No event reported	N=3 studies N=1120 children 1.45 (0.93 to 2.26)

* p<0.005

children with cholera was lower after 24 hours than in children without cholera (131 mEq/l in children with cholera vs. 137 mEq/l in children without cholera), the mean difference between children with cholera treated with reduced osmolarity ORS (130mEq/l) and those treated with standard ORS (132mEq/l) was small.

Combined analysis with earlier trials

When all data on children with cholera who were given a reduced osmolarity ORS (sodium 70-75 mEq/l, glucose 75-90 mmol/l, osmolarity 245-268mOsm/l) (12-14) were pooled, there was a small, but statistically significant reduction, in mean serum sodium at 24 hours in patients receiving reduced osmolarity ORS when compared with those given standard ORS (mean difference 0.8 mEq/l, 95% CI 0.6 to 1.0) (Table 5). Although the relative risk of having a serum sodium concentration below 130 mEq/l at 24 hours was not statistically significantly increased in recipients of reduced osmolarity ORS (RR=1.8, 95% CI 0.9 to 3.2), the CI was consistent with the possible doubling also reported for adults with cholera. No child in these studies who developed hyponatraemia, became symptomatic. Stool output at 24-hours was not different between treatment groups in children with cholera in the multicentre study. In the other two studies, however, stool output was reduced by about 30% in children with cholera who were treated with reduced osmolarity ORS.

Conclusions

(i) For children with acute non-cholera diarrhoea, reduced osmolarity ORS solutions (215-245 mOsm/l) with 75 mEq/l or less of sodium and 75-90 mmol/l of glucose are safe. When compared with standard ORS solution, these solutions were associated with reduced stool output, reduced vomiting and, especially, reduced need for unscheduled IV therapy. With regard to reduced stool output and reduced vomiting, this benefit may be somewhat greater for solutions with <75 mEq/l sodium (210-260 mOsm/l) than for a solution with 75 mEq/l sodium (245 mOsm/l). However, in terms of reduced need for unscheduled IV therapy, the benefit was similar for solutions with 75 mEq/l sodium (245 mOsm/l) and for those with <75 mEq/l sodium (210-260 mOsm/l).

(ii) For children with cholera, reduced osmolarity ORS solutions (245-268mOsm/l) containing 70-75 mEq/l of sodium and 75-90 mmol/l glucose were at least as effective as standard ORS and, although further data should be obtained during routine use, appeared to be safe.

Table 5

Comparison of serum sodium values at 24 hours in children with cholera treated with reduced osmolarity ORS or standard ORS¹.

Author	No. analysed: WHO ORS/RED. OSM ORS	Osmolarity of RED. OSM ORS (mOsm/l)	Serum sodium at 24 hours		Study weight in pooled analysis (10)
			Mean serum sodium with WHO ORS: MEq/l (sd)	Mean reduction in serum sodium with RED. OSM ORS: mEq/l (se ²)	
Dutta et al. (17)	20/19	260	133 (4)	0 (2.09)	0.051
CHOICE (16)	32/26	245	132 (5)	-2 (1.74)	0.061
Alam et al. (18)	16/19	245	136 (1)*	1 (0.12)	0.888

* geometric mean (sd).

Pooled analysis:

- Estimated mean serum Na at 24-hour for patients given standard WHO ORS: 136 mEq/l
- Mean reduction in serum sodium for patients given reduced osmolarity ORS solution: 0.8mEq/l, 95% CI 0.2 to 1.4

¹ The very large weight of the study by Alam is explained by its standard deviation, which is, surprisingly, 4 to 5 times smaller than in the other two studies. If this study were zero-weighted, the pooled analysis of the other two studies would give an estimated mean serum sodium at 24-hour of 132 mEq/l for patients given standard WHO ORS and a mean reduction in serum sodium of 1.1 mEq/l for patients given reduced osmolarity ORS solution (95% CI -0.8 to 3.0).

Decision analysis

A decision analysis model to evaluate possible economic benefits of using reduced osmolarity ORS in place of standard ORS was considered. Assumptions used in the analysis were based on consensus and results of randomized clinical trials (where available) concerning (i) the incidence of unscheduled intravenous fluid therapy in patients given standard or reduced osmolarity ORS (15% for standard ORS, 9% for reduced osmolarity ORS; range tested, 0%-100%), (ii) the probability of seizures in patients who develop hyponatraemia (1%; range tested, 0%-20%) and, (iii) the probability of death when intravenous fluid therapy is not available for patients in whom dehydration is not corrected by oral therapy, or recurs during therapy (50%; range tested, 1%-100%). A revised model was developed that also included costs to the health care system for standard and reduced osmolarity ORS, intravenous fluid therapy, evaluation and treatment of seizures, and death.

The model was constructed as a decision tree with standard ORS and reduced osmolarity ORS as the two options, with a time horizon of two days. The constructed model, where possible, was biased against reduced osmolarity ORS. The probability of needing IV under standard ORS therapy was taken as 0.15, based on the recently published meta-analysis (19). The reduction of 30 % in the need of IV if given reduced osmolarity ORS was based on the same source. The probability of IV access was taken as 0.50, based on opinion of the assembled experts. The probability of death, given the need for IV therapy, but none available, was taken as 0.50, also based on the opinion of the assembled experts. The probability of seizures, when given reduced osmolarity ORS therapy, was taken as 0.01, the upper limit of rates observed in all clinical trials of reduced

osmolarity ORS indexed in Medline. Standard ORS therapy was deemed not to lead to any electrolyte-based morbidities. The following costs were included, all based on expert opinion:

Cost of reduced osmolarity ORS per patient	US\$ 0.50
Cost of standard ORS per patient	US\$ 0.50
Cost of IV therapy per patient	US\$ 10.00
Cost of seizure diagnostic and treatment	US\$ 5.00
Cost of death, to health system	US\$ 1,000.

All results were checked by one-way and two-way sensitivity analyses on all variables.

Comparing the reduction in need for intravenous fluids, the incidence of seizures, as well as costs (excluding the start-up cost of implementing the program), the decision analysis model favoured the reduced osmolarity ORS in all comparisons. Specifically, a total of 14,000 deaths per million episodes of diarrhoea with some dehydration (moderate dehydration) would be avoided with the reduced osmolarity ORS, by reducing the number of treatment failures. This would be associated with a possible addition of 10,000 seizures per million episodes of diarrhoea with some dehydration, almost all in young children. In other words, the estimated number of seizures per death averted would be 0.7. This could result in a cost savings of \$500 per death averted, or \$7.1 million per million episodes. Using sensitivity analysis, reduced osmolarity ORS was always preferred, regardless of changes in the rate of deaths with this model.

Consensus Statement

The meeting concluded with unanimous agreement on the following points:

1. The efficacy of glucose-based ORS for treatment of children with acute non-cholera diarrhoea is improved by reducing sodium to 60-75 mEq/l, glucose to 75-90 mmol/l, and total osmolarity to 215 to 260 mOsm/l. With available data it is not possible to differentiate between the efficacy of ORS solutions containing less than 75 mEq/l of sodium and that of ORS solution containing 75 mEq/l of sodium, as the reduced need for unscheduled intravenous infusion is similar with both of these formulations. Solutions containing 70 to 75 mEq/l of sodium and 75 to 90 mmol/l of glucose for a total osmolarity of 245 to 260 mOsm/l (the only ones tested in children with cholera) also appear to be safe and effective for use in children with cholera.

2. Reduced osmolarity ORS with 75 mEq/l sodium, 75 mmol/l glucose, and total osmolarity of 245 mOsm/l is as effective as standard ORS in adults with cholera, but is associated with an increased risk of transient, asymptomatic hyponatraemia. This reduced osmolarity ORS may be used in place of standard ORS for treatment of adults with

cholera, but further monitoring is required to better assess the risk, if any, of symptomatic hyponatraemia.

Based on these conclusions and recognising

- the programmatic and logistic advantages of using a single solution around the world for all causes of diarrhoea in all ages,
- that reduced osmolarity ORS solution with 60 mEq/l of sodium does not seem to be significantly better than reduced osmolarity ORS solution containing 75 mEq/l of sodium,
- that reduced osmolarity ORS with 75 mEq/l of sodium and 75 mmol/l of glucose is effective in adults and children with cholera, and
- that safety data in patients with cholera, while limited, are reassuring,

the group of experts recommended that the policy of a single solution be maintained, and that this ORS solution contain 75 mEq/l of sodium and 75 mmol/l of glucose, and have a total osmolarity of 245 mOsm/l.*

* This formulation falls within the ranges defined by the WHO's Programme for the Control of Diarrhoeal Diseases (CDD) in March 1992 for a safe and efficacious oral rehydration solution, which remain unchanged:

The total substance concentration (including that contributed by glucose) should be within the range 200-311 mmol/l

The individual substance concentration of:

Glucose	should at least equal that of sodium, but should not exceed 111 mmol/l
Sodium	should be within the range of 60-90 mmol/l
Potassium	should be within the range of 15-25 mmol/l
Citrate	should be within the range 8-12 mmol/l
Chloride	should be within the range 50-80 mmol/l

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