Recent Developments in Oral Replacement of Fluid and Electrolyte Losses

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Oral rehydration therapy (ORT), using a solution of glucose and three salts (ORS) is an elegant and deceptively simple therapeutic technology, to treat or prevent dehydration from diarrhea, that stood the test of time over the past 25 years of use. It contributed substantially to the dramatic global reduction in mortality from diarrheal diseases during this period (1). However, its use does not make diarrhea any less severe or stop it sooner (2), which encourages large-scale use of ineffective and sometimes harmful medicines. Based on a conceptual framework (3,4) WHO in the early 80’s launched studies to develop a more absorption efficient improved ORS formula which could make diarrhea less severe and/or have other clinical benefits. During the past 20 years many studies were carried out to develop an improved ORS and several reviews have summarized the results (5–8). Two approaches were used, (i) modifying the amount and type of organic carriers used in ORS to promote better absorption of salt and water (e.g., combining glucose or maltodextrins with amino acids like glycine or l-alanine or l-glutamine), and (ii) reducing the osmolarity of ORS solution to enhance absorption by osmotic flow of fluids and avoid the adverse osmotic penalty due to hyperosmolarity (e.g., by reducing the concentration of glucose and salts or by replacing glucose with a complex carbohydrate).

An important mechanism mediated by the cotransporters (membrane transport proteins), is the coupled absorption of sodium and organic solutes notably glucose from the small intestine. Historically, a century ago a Scottish physiologist Weymouth Reid (9), using dog intestinal loops, showed enhanced sodium absorption in the presence of glucose. In the late 1960s, this phenomenon was exploited simultaneously by two teams of scientists at Dhaka, Bangladesh and Kolkata, India to develop ORT; they used cholera patients as a model of secretory diarrhea. This discovery is not a scientific curiosity to be restricted to well-supervised medical establishments; it was convincingly demonstrated by its successful use in the field by a team of investigators from Kolkata among refugees crossing in millions into India during the Bangladesh war of independence in 1971 (10). To launch the World Health Organization (WHO) Global Program of Diarrheal Disease Control in 1979, health planners and decision makers put this demonstration to good use.
COMPOSITION OF ORAL REHYDRATION FLUIDS

Early on, planners and implementers of the global Diarrheal Disease Control Program (mainly WHO and United Nations Children’s Fund [UNICEF]) insisted on using a single formulation of ORS for universal use for operational reasons. Given the difference in the pattern of disease due to acute diarrhea in infants (largely due to rotavirus and diarrheogenic Escherichia coli) and in adults with cholera, it became necessary to adapt one ORS formula for all ages and in diarrhea of diverse etiology (11).

IMPROVED ORAL REHYDRATION SOLUTIONS: CONCEPTUAL FRAMEWORK

Promising results from the use of a glucose-based ORS with an added amino acid (glycine) in actively purging cholera in adults and children (12,13), led to the concept of an improved ORS (initially named “super ORS”) (3,4) as stated previously. Conceptually an improved ORS solution should not only replace fecal losses of water and salts but also induce absorption of salts and water that accumulate in the intestinal lumen due to the disease process back into the body fluids and thus reduce the amount and rate of purging, i.e., make diarrhea less severe. In addition, it may stop diarrhea sooner by reducing the flow of fluid from the small intestine into the colon below its absorptive capacity. Such an ORS could then be promoted as an “antidiarrhea medicine.”

OSMOTIC FORCES IN THE GUT LUMEN AND EXPERIMENTAL ORAL REHYDRATION SOLUTION FORMULATIONS

Organic solutes in ORS that are not absorbed create an adverse osmotic effect in the gut lumen and reduce the efficiency of the solution. The rate of glucose absorption in acute diarrhea has an upper limit that may even be lower in infants and small children (14,15). It was thought that possible ways to minimize the adverse osmotic effects of an ORS formulation would be to: (i) use a combination of organic solutes that are absorbed efficiently and relatively independently of each other, e.g., glucose and neutral amino acids (e.g., glycine, l-alanine and l-glutamine); and (ii) use polymers of organic molecules, e.g., glucose polymers like maltodextrins which should exert less osmotic pressure and on hydrolysis are expected to be absorbed at a favorable rate.

INDICATORS OF ABSORPTION EFFICIENCY

The indicators of absorption efficiency of ORS used in most studies are rate of stool output, which is usually reported as the first 24 hours of stool output per kilogram of body weight; diarrhea duration; and total diarrheal stool output per kilogram body weight until cessation of diarrhea. This last indicator is the composite
of stool rate and diarrhea duration and is a powerful summary measure for evaluation of absorption efficiency of an ORS solution.

IMPROVED ORAL REHYDRATION SOLUTIONS: FIRST-GENERATION STUDIES

Approaches Used

i) One approach was to add an amino acid, glycine, to glucose ORS that followed encouraging results with similar solutions in cholera (12,13). Although the solutions were hyperosmolar, it was expected that glucose and glycine with independent absorption mechanisms would be absorbed fast and create minimal osmotic problems. Subsequently, amino acids L-alanine and L-glutamine were used in place of glycine because of their better absorption efficiency.

ii) The second approach was to combine glucose polymers and amino acids to replace glucose in ORS. Apart from the advantage of using a maltodextrin for its low osmolarity, this formulation should have the added advantage of achieving enhanced sodium absorption independently by amino acids.

iii) The third approach was to replace glucose in ORS by glucose polymers such as maltodextrins in larger amounts; they have low initial osmolarity and can deliver increased amounts of substrate, i.e., glucose, on hydrolysis. However, effective osmotic forces in the small intestinal lumen will depend on the rates of hydrolysis of polymers and of absorption of glucose.

iv) The fourth approach was to use a cooked cereal powder, mainly rice to replace glucose in ORS. This approach followed the serendipitous finding that use of an ORS containing 50 g/l of cooked rice powder in place of glucose was associated with a clinically significant reduction in purging rate compared with standard glucose ORS (16). Such a solution contains complex starch and some proteins that on hydrolysis would liberate glucose and some amino acids. Osmolarity of the solution is low and a larger amount of glucose is delivered in the intestinal lumen on hydrolysis. Any undigested starch is likely to be fermented in the colon to short-chain fatty acids, which would also stimulate absorption of electrolytes and water.

The results of studies on these improved ORS have been summarized in several overviews and meta-analysis (5–7). The findings of the studies are briefly summarized.

Oral Rehydration Solution With Added Amino Acids

Three actively absorbed neutral amino acids have been studied. They are glycine (and its peptide glycy-glycine), L-alanine, and L-glutamine. These were added to glucose-based or maltodextrin-based ORS. Results of a large number of controlled clinical trials were reviewed (7).
Treatment of Cholera

ORS solutions with added glycine or L-alanine or L-glutamine were substantially more absorption-efficient than standard ORS for treatment of cholera; this occurred despite the solutions being hyperosmolar (350 to 430 mosm/l). Patients treated with these formulations had a minimum of 30% reduced purging rate than those treated with standard glucose ORS.

Treatment of Children With Acute Noncholera Diarrhea

Amino acid–containing ORS formulations were not any more absorption efficient than standard ORS in infants and young children with acute noncholera diarrhea (largely due to diarrheogenic E. coli and rotavirus). This lack of efficacy appeared to be due to the solution’s high osmolarity, which may have offset the beneficial effect of amino acid–mediated improved absorption. This apparent adverse osmotic effect in infants could be related to the patient’s age or the etiologic agents of diarrhea or both.

Maltodextrin Oral Rehydration Solution

An ORS with 50 g/l of minimally hydrolyzed maltodextrin in place of glucose (20 g/l) was no more effective than standard ORS in infants and young children with acute noncholera diarrhea, and yet its osmolarity was low (227 mosm/l) to start with (7). In one of these clinical trials, a substantial proportion of children receiving either standard glucose ORS or maltodextrin ORS had an apparent increase in stool output and evidence of temporary glucose malabsorption. This suggests that, at least in some infants and young children, even 20 g/l of glucose may exceed their absorptive capacity. Maltodextrin ORS was not evaluated in cholera.

To conclude, none of the amino acid– or maltodextrin-containing ORS formulations tested could be considered a better alternative to standard ORS.

Cereal-Based Oral Rehydration Solution Formulations

In a study evaluating the scope of using popped rice powder (50 g/l) as a practical alternative to glucose in ORS, a clinically significant reduction in purging rate in children with cholera and cholera-like diarrhea, was shown in the group receiving rice-ORS compared to those given standard glucose ORS (16). Since then, many trials compared the efficacy of cereal-based ORS (mostly rice-based) with standard ORS and the results have been reviewed (6,7,17). Early on, rice powder (50 g/l) was either cooked for about 10 minutes and salts were added in concentration similar to standard WHO ORS or a powder of popped rice (without further cooking) was mixed with the same amount of salts and water. More recently industrially produced packets of precooked rice powder plus salts have also been used. In a limited number
of studies, other cereals such as wheat, maize, sorghum, and millet were used and results were similar to those with rice ORS.

A meta-analysis of results of 13 randomized controlled trials (1992) comparing rice-based ORS (50 to 80 g/l rice powder) with standard glucose-ORS recommended by WHO (6) included 531 adults and 424 children with cholera or cholera-like severe diarrhea, and 344 infants or young children with acute noncholera diarrhea. Results of this meta-analysis are summarized.

(i) Cholera patients, both adults and children, treated with rice-ORS had substantially reduced purging rate; in the rice-ORS group, stool output was reduced by 34% (95% CI: 25% to 43%) compared to glucose ORS; and

(ii) in infants and young children with acute noncholera diarrhea given rice-ORS, 24-hour stool output was reduced by 18% (95% CI: 6% to 30%) compared to children given glucose-ORS.

Rice-ORS in infants below 6 months of age: Because rice may not be fully digested by very young infants, two studies compared rice-ORS with glucose ORS in infants younger than 6 months old (18,19). Rice-ORS was as effective as glucose ORS in young infants; there was a trend toward reduced stool output, but the differences were not statistically significant.

Rice-ORS in severely malnourished children: In two randomized trials in 214 severely malnourished children with acute noncholera diarrhea (20,21), rice-ORS was as effective as glucose-ORS in one and more effective in the other (21); a trend toward reduced stool output in rice-ORS treated group (20) was reported in one and in the other it was significantly reduced (21).

A revised meta-analysis (7) of rice-ORS trials in children (nine studies on a total of 1,172 children) showed that stool output was only reduced by 7% (95% CI: -3%, 15%) which did not achieve statistical significance. More recent studies in children (n = 828) used a more aggressive feeding regimen that included a cereal-based (usually rice) food. A more recent meta-analysis (17) that included an additional 1,091 children from two recent studies (Faruque ASG and Mahalanabis D, unpublished), i.e., on a total of 2,263 children, showed similar results.

SOME CONCLUSIONS ON RICE-BASED ORAL REHYDRATION SOLUTIONS

i) Rice-ORS substantially reduces diarrhea (by one third) in adults and children with cholera;

ii) Efficacy of rice-ORS is at least as good as glucose-ORS in acute non-cholera diarrhea in children given food (containing cereals) shortly after rehydration; in studies where supervised active frequent feeding was not implemented, rice-ORS was shown to be superior to glucose-ORS; however, the effect size was not as large as in that in cholera; and

iii) Rice-ORS is as effective as glucose-ORS in infants younger than 6 months
old and in severely malnourished infants and children; use of rice-ORS is not associated with any undesirable side effects or complications.

GLUCOSE-ORAL REHYDRATION SOLUTION WITH REDUCED OSMOLARITY

Concern was expressed about the reported clinically significant glucose malabsorption in a proportion of children treated with standard glucose ORS (7). It was thought that the concentration of glucose in WHO-ORS might exceed the upper limit of glucose absorption rate in a significant proportion of infants and small children with acute noncholera diarrhea. Early physiologic experiments suggested that the upper limit of the glucose absorption rate might be a good deal lower in infants and small children (14,15). Based on experimental studies (22-25) in animal models of diarrhea, mostly toxin-induced cholera except for one that also used a rotavirus model in rats (25), several investigators in recent years have proposed that an ORS made hypoosmolar by reducing both the glucose and sodium concentration may be more absorption-efficient. This is based on the observation that water absorption is substantially higher from such solutions and that sodium absorption would be sufficient to meet the needs of infants and children with dehydration due to acute diarrhea, provided the concentration of sodium is 60 mmol/l or higher. The European Society for Pediatric Gastroenterology and Nutrition recommended an ORS solution (26) for infants and children in developed countries with a sodium concentration of 60 mmol/l and a reduced glucose concentration; however, their major concern was sodium concentration, which was thought to be high in WHO-ORS for young infants. Furthermore, in a non-randomized open trial, Rautanen and colleagues (1993) reported reduced diarrhea frequency and shorter hospital stay with an ORS made hypoosmolar by reducing the glucose and sodium concentration (27). Since then a large number of studies have been undertaken to evaluate glucose ORS formulations made hypoosmolar by reducing the concentration of sodium and glucose (28-43). These included two multicenter trials supported by WHO.

REDUCED OSMOLARITY GLUCOSE ORAL REHYDRATION SOLUTION TRIALS

A large number of controlled clinical trials used an ORS formulation in which osmolarity was reduced by lowering the glucose and sodium concentration to 75 to 90 mmol/l and 60 to 75 mmol/l, respectively, with a total osmolarity of 225 to 245 mmol/l (Table 1). In a WHO/ICDDR,B consultative meeting in Dhaka, Bangladesh in 1994 data from studies conducted with these formulations (including unpublished data provided by the investigators) were reviewed (45). It was concluded that, reduced osmolarity ORS significantly reduced the stool output and diarrhea duration when compared to standard ORS in infants and children with non-cholera diarrhea. Some benefit was also shown in a study in adults with severe disease due to cholera.
TABLE 1. Composition of reduced osmolarity ORS solutions used in published studies compared to the standard solution

<table>
<thead>
<tr>
<th>Components (mmol/l)</th>
<th>Reduced osmolarity ORS</th>
<th>Standard ORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>B&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glucose</td>
<td>75-90&lt;sup&gt;d&lt;/sup&gt;</td>
<td>111</td>
</tr>
<tr>
<td>Sodium</td>
<td>60-70</td>
<td>50</td>
</tr>
<tr>
<td>Chloride</td>
<td>60-70</td>
<td>40</td>
</tr>
<tr>
<td>Potassium</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Citrate/Bicarbonate</td>
<td>10&lt;sup&gt;1&lt;/sup&gt;</td>
<td>30&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calculated osmolarity/l</td>
<td>210-260</td>
<td>251</td>
</tr>
</tbody>
</table>

<sup>a</sup>Used in seven studies including a multicenter trial (29-34, 40).
<sup>b</sup>Used in one study (28).
<sup>c</sup>Used in five studies including the recent multicenter trial by WHO (35-39).
<sup>d</sup>One formulation used sucrose in place of glucose, and another used glucose + L-alanine.

(43), but data were insufficient to reach firm conclusions with regard to the possible risk and benefits of such an ORS in cholera. Given the WHO's preference for a single reduced osmolarity ORS solution suitable for both adults and children, multicenter trials were initiated following this meeting to evaluate a reduced osmolarity ORS with glucose and sodium concentrations of 75 mmol/l each and an osmolarity of 245 mosm/l (Table 1) both in adults with cholera and in children with non-cholera diarrhea. The rationale for this composition was to provide a sodium concentration only modestly less than that in standard ORS, with which it was considered important to treat adults with cholera.

REDUCED OSMOLARITY ORAL REHYDRATION SOLUTION IN CHILDREN: OVERVIEW

A recent meta-analysis (8) that included this recent multicenter trial (36) summarized the results of reduced osmolarity ORS trials in children. The results of this systematic review are summarized in Table 2. Reduced osmolarity ORS was more effective than standard WHO-ORS in the first-time treatment of children with diarrhea. It reduced the need for unscheduled intravenous infusion (by 39%), stool output during hydration (by 19%), and the number of patients with vomiting during rehydration (by 29%). There was a trend for a nonsignificant increased incidence of hyponatremia (i.e., serum Na<sup>+</sup> < 130 mmol/l) in the children treated with reduced-osmolarity ORS solution. All these studies were conducted in children admitted to hospitals with dehydration. Oral rehydration solutions are also used to prevent dehydration both in clinics and in homes and, in a recent community-based controlled trial in children (44), reduced osmolarity ORS was as effective as standard ORS. Furthermore, non-breastfed children treated with reduced osmolarity ORS had significantly shorter diarrheal episodes.

In a recent consultative meeting convened by WHO and UNICEF in New York
in July 2001, all available data (both published and unpublished) on reduced osmolarity ORS trials were reviewed with particular attention to policy implications (46). In this meeting, data from the recent multicenter trial of reduced osmolarity ORS containing 75 mmol/l sodium and 75 mmol/l glucose in children (36) were also reviewed separately. This study was conducted in five countries and enrolled 675 children 1 to 24 months old. In contrast to the meta-analysis summarized previously (8), this study did not show any difference in stool output between the two treatment groups. However, as in earlier studies, the need to use unscheduled intravenous (IV) fluids was reduced by 40% among the reduced osmolarity ORS group. The incidence of hyponatremia was similar in the two groups. The comparative data between trials using a reduced osmolarity solution containing 75 mmol/l of sodium and those using 50 to 70 mmol/l of sodium (46), were compared by WHO (Table 3). It shows that the need for unscheduled IV therapy and occurrence of vomiting were reduced in children receiving either of these reduced osmolarity ORS solutions compared to standard ORS. Stool output was reduced in children treated with ORS containing 70 mEq/l or less sodium but it was not so for the group treated with ORS containing 75 mEq/l sodium.

### REDUCED OSMOLARITY ORAL REHYDRATION SOLUTION IN CHILDREN WITH CHOLERA

A small subgroup of patients enrolled in the recent multicenter study (9%) had culture-proven cholera (36). In this subgroup, unscheduled IV therapy was lower in children treated with reduced osmolarity ORS than in children receiving standard ORS (30% vs. 44%). Stool output at 24 hours was not different between the two

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**TABLE 2. Reduced osmolarity ORS trials in children: meta-analysis of 15 randomized controlled trials**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Percent change&lt;sup&gt;b&lt;/sup&gt; (95% CI in percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool output&lt;sup&gt;c&lt;/sup&gt;</td>
<td>934</td>
<td>-19.3%&lt;sup&gt;d&lt;/sup&gt; (-11.6% to -26.3%)</td>
</tr>
<tr>
<td>Vomiting&lt;sup&gt;a&lt;/sup&gt;</td>
<td>657</td>
<td>-29%&lt;sup&gt;d&lt;/sup&gt; (-8% to -45%)</td>
</tr>
<tr>
<td>Unscheduled IV infusion</td>
<td>1049</td>
<td>-39%&lt;sup&gt;d&lt;/sup&gt; (-19% to -53%)</td>
</tr>
<tr>
<td>Hyponatremia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>562</td>
<td>+45%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Controls received WHO-ORS.  
<sup>b</sup> Negative number favors study group.  
<sup>c</sup> We calculated the ratio of the geometric means and their confidence intervals from the standardized mean difference on log scale given by the authors.  
<sup>d</sup> p < 0.05.  
<sup>e</sup> Derived from the odds ratios and their confidence intervals provided by the authors.  

From Gutierrez et al. (8).
Table 3. Comparison of studies of reduced osmolality ORS solution using a sodium concentration of 60–70 mmol/l with those using a sodium concentration of 75 mmol/l: pooled analysis by WHO

<table>
<thead>
<tr>
<th>Variable</th>
<th>ORS with 50–70 mmol/l of sodium vs WHO-ORS</th>
<th>ORS with 75 mmol/l of sodium vs WHO-ORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent change (95% CI)</td>
<td>percent change (95% CI)</td>
</tr>
<tr>
<td>Stool output</td>
<td>(n=771)</td>
<td>(n=1049)</td>
</tr>
<tr>
<td></td>
<td>-31%</td>
<td>-12%</td>
</tr>
<tr>
<td></td>
<td>(-2% to -51%)</td>
<td>(-29% to 16%)</td>
</tr>
<tr>
<td>Unscheduled IV therapy</td>
<td>(n=678)</td>
<td>(n=1175)</td>
</tr>
<tr>
<td></td>
<td>-35%</td>
<td>-44%</td>
</tr>
<tr>
<td></td>
<td>(-59% to 0%)</td>
<td>(-20% to -61%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>(n=270)</td>
<td>(n=1031)</td>
</tr>
<tr>
<td></td>
<td>-51%</td>
<td>-26%</td>
</tr>
<tr>
<td></td>
<td>(-9% to -73%)</td>
<td>(-5% to -42%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>(n=139)</td>
<td>(n=1120)</td>
</tr>
<tr>
<td>(Serum sodium &lt;130 mmol/l)</td>
<td>No event reported</td>
<td>+45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-7% to +126%)</td>
</tr>
</tbody>
</table>

*a*For either study group, control groups received standard ORS recommended by WHO (46).

*b*Negative number favors the study group.

*c*We calculated the ratio of the geometric means from the standardized mean difference in log scale reported by the authors.

*d*Derived from the odds ratios and their confidence intervals provided by the authors.

Treatment groups in children with cholera. However, in the other two studies (37,38) in whom ORS with 70 mEq/L or less of sodium was used, stool output was reduced by 30% in children with cholera.

**Use of amylase-resistant starch in oral rehydration solutions**

In a controlled clinical trial (47), Ramakrishna and colleagues showed that adding an amylase-resistant starch (50 g/l) to standard glucose ORS markedly increased its absorption efficiency, and compared to standard ORS in adult cholera. In the experimental group, the mean stool output during 12 to 48 hours was reduced by 40% and diarrhea duration by 38%. The starch used was derived from a specific variety of corn and when ingested uncooked, 50% to 70% of the starch is not digested in the small intestine and it is fermented and converted to short-chain fatty acids in the colon. As discussed previously, short-chain fatty acids stimulate absorption of salts and water from the colon. Additional studies are required to understand the scope and limits of using amylase-resistant starch in improved ORS.

**Concluding remarks**

The efficacy of glucose-based ORS for the treatment of children with acute diarrhea is improved by reducing the sodium level to 60 to 75 mEq/l and glucose to 75
to 90 mmol/l, and total osmolarity to 215 to 260 mosm/l. The most impressive benefit was the reduced need for unscheduled IV therapy. This finding has implications for healthcare resources such as hospital infrastructure, trained personnel, supplies, and logistics. Furthermore, reduced osmolarity ORS with a sodium concentration in the lower range (e.g., 60 to 70 mEq/l) also reduces the stool output. While reduced osmolarity ORS solutions are also efficacious in children with cholera, the risk of some degree of asymptomatic and transient hyponatremia needs to be addressed. Similar considerations also apply to adults with cholera. The policy issues arising out of these new findings are being discussed in the article by M K Bhan.

I would like to see more studies on (i) a cereal rice-based ORS with a lower sodium concentration, and (ii) a reduced osmolarity ORS containing amylase-resistant starch.

REFERENCES


Dr. Roger J. Glass: I have some questions about the decrease in vomiting associated with the new ORS. I often think of vomiting as a characteristic of viral gastroenteritis and particularly rotavirus and calesy virus and not other bacterial diseases, and that the mechanism of vomiting in these diseases is different. It’s central as opposed to the dehydration that’s intestinal and so my question is: why do you think oral therapy decreases vomiting? Is there another mechanism involved here? Is there something else involved?

Dr. Dilip Mahalanabis: I don’t think we know why vomiting is reduced. It seems that the better absorption efficiency may have had something to do with it, but we do not know the mechanism behind it. Our studies did not look at mechanisms, which seems wanting.

Dr. Roger J. Glass: If you fail and go on to IV treatment, which is your largest indicator, is the reason that they’re put on IV treatment due to vomiting, so that they don’t tolerate the rehydration? Is that also linked?

Dr. Dilip Mahalanabis: Some of them surely were due to vomiting, but the decision is made by the clinicians on the basis that the child became more dehydrated or the child could not be hydrated with ORS and then should be put on IV. This decision was independent of the way the ORS was given and vomiting obviously would be one of the reasons especially with persistent prolonged vomiting, which in several instances was also reflected in more dehydration or the inability to maintain hydration. So primarily they look for the ability to maintain hydration or the child becoming more dehydrated and one of the reasons for that would be, of course, vomiting or the inability to take enough ORS.

Dr. Roger J. Glass: If vomiting is related to etiology, then the new rehydration therapy might behave differently in countries like the United States, where you have lots of viral diarrheas with lots of vomiting, as opposed to studies in Bangladesh, where the viral diarrheas are minority and the other non-vomiting etiologies are more predominant.

Dr. Dilip Mahalanabis: I don’t recall whether the rotavirus diarrhea was separately analyzed for vomiting. So I don’t think they looked at it, but it’s worth looking at. If you look at the rotavirus diarrhea and it shows reduced vomiting also with hypoosmolar ORS, then they’d be surely effective. It is recommended for viral diarrheas as well.

Dr. George Fuchs: I think certainly osmolarity can also effect gastric emptying, so independent of the etiology, that might be a possible explanation for the difference in vomiting.
meta-analysis by Hahn and colleagues indicates a percent difference that is significant for stool output, but if you look at the absolute values, it's rather small. And they did publish a table, in the electronic version of that meta-analysis that wasn't available for the print version. If you look at the different studies, some studies showed it to be quite inconsistent, and the comment I would make is that the conclusions based on that were drawn in a different way. Usually we do a meta-analysis to try to look and see if there's a direction that would benefit from it, then we would do a randomized controlled definitive trial. However, this was done in reverse, because the so-called definitive trial was the multicenter trial, which was actually included in the meta-analysis. Now that study didn't show any difference in stool output, so I think one conclusion could be that the reduction in stool output is small if at all with that preparation of the reduced osmolarity ORS, and I think this has some impact on the programmatic side. The whole reason to develop these reduced osmolarity ORS use the main outcome of interest was reduced stool output, primarily because the ORS youth rates were so low and it was felt that the reduced osmolarity ORS might reduce stool output so much that the resistance by parents to use ORS would then go away. I'm not sure if the magnitude of the reduction, if there is any reduction, is really going to achieve that, and I just wondered if you wanted to comment on that, Dilip, the programmatic aspect.

Dr. Dilip Mahalanabis: I have also shown the data on those who received ORS, which used 50 to 70 compared to 75 mmol/l sodium, and if you look at the data, the stool output reduction figure was there. So, you are right that the multicenter trial in children with an ORS containing 75mmol/l of sodium and glucose did not show any significant effect on stool output. The trend was there but didn’t show any significant effect, but the comparison, which was made has not been published, I have taken the liberty of showing it, because it’s going to be published in a document by WHO, which is already finalized, where they compared all the studies, including the meta-analysis with sodium 75, with the studies which used lower sodium concentrations, and you could see that there was a modest but not too bad a reduction in the stool output. And in Hahn’s meta-analysis, if you look at all the 11 studies, all of them had the same trend, except for one, which perhaps should not have been included, as it was a study where the investigators used a maltodextrin and sodium 90 ORS and Hahn’s group included this, calling it a hypoosmolar ORS, which it really was not. We already knew that that type of ORS doesn’t help in children. So if you take that out, all the other studies had the same trend of reduced stool output. It’s true that the 75 mmol/l each of sodium and glucose was a large study and it didn’t show any effect on fecal output. But if you take the other studies, which used a lower sodium concentration ORS, the effect on the fecal output was significant, and I would say a moderate reduction.

Dr. S. K. Mittal: Dr. Mahalanabis, I have three to four questions, so if you will permit, I’ll ask them one by one. One is: What is the sort of relationship between osmolarity and the stool output? We know that towards the upper end of the osmolarity up to a certain limit the output will start coming down, meaning that the absorption will be much more. Is there a lower limit for this?

Dr. Dilip Mahalanabis: Some information has been provided by experimental studies. I think Michael can talk about that more, that if you use a dilute solution at all, it may not be advisable to use a sodium less than 60 mmol/l, because you cannot go on doing studies at lower and lower levels of sodium. While you cannot say from human studies, it seems from animal experiments, if you reduce sodium below 60, you lose the advantage of reducing the osmolarity. Regarding these animal experiment studies, I think Professor Farthing might comment on that one.

Dr. S. K. Mittal: Is it related to the osmolarity part? That’s what I want to know.
Dr. Dilip Mahalanabis: It is difficult to separate the two; then you may do experiments where you use some artificial substances which will adjust osmolarity and will not be absorbed and in some experimental studies, we used such molecules to adjust the osmolarity, which would not be absorbed, but apparently those additions distorted the physiology to the extent that it was no longer advisable to use them. It is very difficult to fix the one without changing the other in in vivo dynamic situations.

Dr. S. K. Mittal: Can we dissect the effect of low sodium versus low osmolarity? If you go through a licensed textbook, the average stool losses of sodium is just about 50 to 60. Why do we want to give more sodium than what we are losing in an infant?

Dr. Dilip Mahalanabis: Okay, let me answer your question perhaps partially. It was not a disease model, but a rat perfusion model, which we also used many years ago; I got one of my research fellows to do a perfusion study in this model. We perfused two solutions where, in one, we reduced glucose and in the other solution we reduced sodium, keeping the other one at the same level and then the isotonic solution was perfused in the rats. Reducing either glucose or sodium increased absorption of water, but I was surprised to note that it also increased in absolute terms the absorption of sodium from both situations. But the magnitude of the effect of reducing sodium was substantially higher than the effect of reducing glucose. Now the trouble is, this is again a non-disease model, so you have to extrapolate from a non-disease model; the study was not extended to a disease model. This has not been published. This study was a fall out of the WHO consultative meeting on reduced osmolarity ORS at ICDDR, Dhaka.

Dr. S. K. Mittal: One of the clinical problems we face in our clinical testing is the acceptability of the oral rehydration solution and the infants would tend to accept something with a sweet. If we reduce the glucose from 110 to 75, I think this is something we need to see. What is the acceptability of this? It just might be good physiologically.

Dr. Dilip Mahalanabis: Dr. Bhan is not here, but I think George, you can respond to that very well.

Dr. S. K. Mittal: Are we aware of any studies, where people have used only rice ORS without sodium, without any added electrolyte in it? Would this be beneficial?

Dr. Dilip Mahalanabis: I suspect not, unless there are other sodium sources in the diet the child is having.

Dr. S. K. Mittal: Lastly the question of programmatic. Why should we insist on having a single solution for adult cholera and infant diarrhea? This is something, which is not understandable to me.

Dr. Dilip Mahalanabis: This is a good point and very good but please hold it for the time being and Professor Bhan will address the policy issues on this. I know it is a very explosive topic.

Dr. Veena Kalra: My question pertains to using carrier ORS, particularly when you use glycine ORS in experimental situations. Is there a tendency to develop an increased plasma ammonia in the experimental situation that may have some clinical consequence?

Dr. Dilip Mahalanabis: Well it was not measured, but they were not overly acidotic or problematic. The only problem they had was in some of the studies if the stool output increased with an osmotic diarrhea, they had more dehydration, but we didn't observe any problem with the amount used.

Dr. Abdul Majid Molla: We have been discussing it for the last two decades. In the multi-centre study of hypoosmolar ORS, they have reduced the sodium as well as glucose. Was mass rice-based ORS included in the multi-syndrome study? Number two: these studies are all based on hospital situations. As we all know, roughly about 10% to 15% of the total
diarrheal patients come to hospital, the rest are treated in the community. Is there any community-based data included?

Dr. Dilip Mahalanabis: I apologize for not including the collaborative study between Professor Bhan and the Norwegian group in Africa. In that study, they showed that it is very well taken in the community situation to prevent dehydration; it is as effective as standard ORS and reduces the frequency of diarrhea and duration. And that study has been just published. I’m sorry. I should have covered that one.

Dr. Yong Joo Kim: I have two clinical questions. Rehydration is meant to retain the normal vital signs in kids with urinary output. If you have compared the rehydrating time, was there any difference between the standard ORS and the osmolarity ORS? And the second question is about one of the most difficult aspects of introducing ORS, namely its palatability. If the sugar component of the ORS were lowered, the palatability would be worse. Could you possibly explain your experience or feeling on osmolarity ORS?

Dr. Dilip Mahalanabis: If I understood you, there are two questions. One is the time to achieve full hydration by standard ORS versus lower osmolarity ORS, is it different or has it been studied? To my knowledge, it hasn’t been really looked at from that point of view and studied; so the actual issue here is its ability to hydrate and maintain hydration and so prevent the need for additional intravenous therapy and to reduce the severity of diarrhea, which is reflected in the fecal output. So, that has not been separately studied. This is a good question. The second question is palatability. Now palatability has to be judged by the child’s ability to drink as much as is required by the child. All the studies reported that the acceptability of hypoosmolar ORS is pretty good, and they didn’t have problems, either during hydration or during maintenance, giving enough ORS to keep them in balance. So one has to assume that it is well taken by both adults and children.

Dr. Wolf Endres: My question concerns bicarbonate and citrate. There are some commercially available ORS containing bicarbonate and others with citrate. What is your opinion?

Dr. Dilip Mahalanabis: Apart from the convenience of packaging and shelf-life, they are equivalent. The initial osmolarity of a bicarbonate solution is obviously slightly higher than citrate, because the citrate used is tri-sodium citrate, so the initial osmolarity of the solution is a little less, and regarding citrate, I think the standard recommendation is, you can use either of them in any ORS composition, there’s no particular preference, although there were some earlier studies, which showed that citrate or acetate may be advantageous for better absorption. Majid perhaps you may remember from some of these studies if citrate or acetate showed better results.

Dr. Abdul Majid Molla: In cholera, as well as non-cholera patients conducted in ICDDR,B showed a definite advantage using citrate from most other additional fluids in electrolyte from the gut, especially in cholera patients, but also to some extent in non-cholera patients.

Dr. Michael J. G. Farthing: Dilip, do you think you need citrate at all? If you were treating diabetic ketoacidosis, most of us would not give any base, but just rehydrate with fluid and sodium chloride. Why do we have a base in ORS at all?

Dr. Dilip Mahalanabis: One can argue for not having a base at all, but that hasn’t been extensively studied in clinical situations.

Dr. Shrichandra Bhawnani: So concerning the renal immaturity of a newborn baby up to the age of 3 months, I believe, what kind of oral rehydrating solution should you prescribe for a newborn baby or an infant up to 3 months of age?

Dr. Dilip Mahalanabis: Very good question. Actually if you recall that when the health planners in WHO and UNICEF insisted that we must provide one single solution, I had to scratch my head to work out a treatment modality, which would adapt a single solution for
all situations. The trickiest part was newborns and infants under 3 months and that for them we proposed that you use the same ORS, less of it, but give them other fluids so that in a single recommendation you can incorporate a flexibility for older children, to whom you don’t have to worry about giving as much ORS, but for infants and young infants you use ORS to start with, but you also give other fluids. Trials confirm that it is extremely robust in terms of safety and efficacy and you may recall the classic studies by Daniel Pizzaro; Daniel did those studies in newborns and showed that if you follow this kind of protocol, they don’t have a problem. Arguably one can ask if one deviates from this protocol, what is the danger? It seems to be fairly robust.

**Dr. Denis Barclay:** Please excuse me, Dilip, if I missed it in your presentation, but with respect to the home use of oral rehydration, was there an improvement in the reduction in the duration of diarrhea with the low osmolarity solution?

**Dr. Dilip Mahalanabis:** I think it was more a reduction in the proportion with prolonged diarrhea. I forgot that one, but there was some benefit, although they obviously didn’t measure stool or the stool frequency. In fact, they were looking at duration and there was some benefit and it was well taken; even though they were not dehydrated, they drank it well and actually it worked out exceedingly well in their field situation.

**Dr. George A. Bray:** This is a field quite far from where I usually am, but a question regards the suitability of the molecule fructose transported by the glucose sodium co-transporter. Have people used fructose rather than glucose in the solutions, because it’s sweeter and has a lot of different metabolic pathways in its metabolism?

**Dr. Dilip Mahalanabis:** I believe fructose is absorbed at a slower rate, but absorbed pretty well into facilitated transport and if it is absorbed, as with glucose sodium will be absorbed too. In fact there have been trials with sucrose, which on hydrolysis will produce one molecule of glucose and one molecule of fructose and they were highly successful and there have been trials of hyposmolar ORS using sucrose, which were done by us and others also, and was included in that meta-analysis; it works very well. It has two advantages. The first is that initial osmolarity using sucrose, because it is disaccharide, will be less for the equivalent amount of monosaccharide. Secondly, sucrose is a whole lot sweeter than glucose or fructose; cane sugar is a whole lot sweeter weight for weight than either glucose or fructose; so if you use sucrose then obviously you are in effect using both glucose and sucrose.

**Dr. S. K. Mittal:** I come back to the bicarb-citric thing. If we just go through the disease models, except for the cholera and maybe some other toxigen i.e., diarrhea with a very high purge rate, you do not have much bicarb loss in the intestine. The metabolic acidosis, which you see in dehydrated children, is largely related to volume depletion and not due to the bicarb loss, so I do not know why we should keep on insisting on having bicarbonate in the oral rehydration solution?

**Dr. Malathi Sathiajekaran:** I would like to know whether the sodium glucose ratio, the ideal one is one-to-one, or is it arranged for better absorption of sodium?

**Dr. Dilip Mahalanabis:** It’s a very difficult question to answer, a very good question though. What is the best ratio of glucose to sodium? In actual in vivo situation, let’s try to visualize what happens if we drink an ORS. It goes into the stomach, gets diluted by the stomach fluids then it goes down into the duodenum. Then if it is hypoosmolar, the water is rapidly absorbed and I suspect that because the water is absorbed it becomes isosmolar by the time it reaches the duodeno-jejunal flexure and by then it is isosmolar anyway. At that point, the intestinal fluid with which it mixes has a high sodium concentration, but obviously has less glucose. Now one can speculate that if you give a little more glucose, then by the time it reaches the jejunum, you have far less glucose and more sodium, so it’s very difficult
in an intact human situation to predict what will happen. It will depend on the rate of emptying of the stomach, transit time, then mixing with intestinal fluid, the rate of secretion into the small bowel and it's almost impossible to say what would be the best ratios in human situations. So it has always been a guess work, and people try 1:1 or give a little more glucose in ORS. This has always remained a speculative issue and one can never be sure what is the best ratio of glucose to sodium.