Special Article

RECENT ADVANCES IN ORAL REHYDRATION THERAPY

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Since its earlier description a quarter of a century ago by Captain Robert Phillips(1) various trials have demonstrated that optimally constituted oral rehydration fluid, could replace massive amounts of fluid loss to obtain a positive gut balance for sodium and water in acute secretory diarrhea(2-6). With its successful clinical application in noncholera enteritis in adults as well as for diarrheas of varied etiologies in infants and children(7-17), oral rehydration therapy(ORT) has been described as potentially the most important medical advance of this century(18). It is considered as a major scientific advance of practical importance, a powerful tool for the replacement of dehydration, due to acute diarrhea, an invaluable public health weapon, an essential component of primary care and a useful entry point for other child survival interventions(19). Appropriate feeding during and after diarrhea is an *essential* part of optimal case management with oral rehydration therapy.

The oral rehydration solution (ORS) recommended by the WHO and UNICEF contains glucose (20 g) and three salts–sodium chloride (3.5 g), sodium hydrogen carbonate (2.5 g) or more recently trisodium citrate dehydrate (2.9 g) and potassium chloride (1.5 g) to be mixed with one litre of water to prepare oral rehydration solution. In 90% of patients with dehydration it can reduce the hospital admission rate for treatment of diarrhea by atleast 50%(20,21), reduce diarrheal mortality(22) and limit weight loss(23) when used with appropriate feeding. In addition, ORT using the present ORS formulation is one of the least expensive health interventions(24).

Limitations of the Present ORS Formulations

ORT with the present ORS formulations does not reduce the volume, frequency or the duration of diarrhea(3,4,7,25). This raises the practical problem of its acceptance since a major concern of mothers and health workers during diarrhea is to reduce the frequency and volume of the child's stool. This leads

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to a persistent desire to use antidiarrheal drugs.

Issues and Controversies(26)

The present ORS formula is based on the stool electrolyte losses in cholera and noncholera enteritis, in adults as well as children and comparing them with plasma electrolyte composition. *Table I* summarises the stool electrolyte losses and serum electrolytes in diarrhea of different etiologies.

As seen the composition of oral fluid is more suitable for stool losses in adult cholera patients and it closely resembles plasma.

The issues related to the ORT are numerous and they include (*i*) composition with special reference to sodium and glucose content and osmolality, (*ii*) the packaging, labelling, storage and stability, (*iii*) the effectiveness of the standard ORS versus various commercial preparations, (*iv*) modifications by additives, coloring and flavoring agents, (*v*) ability of mothers to learn to prepare and practice ORT at domestic level using household measures for water and other ingredients, (*vi*) limitations of ORT, improved ORS formulations, food based or with chemical additives, and (*vii*) suitable fluids for different phases of rehydration and maintain and feeding along with ORT . A few of these points are discussed in detail.

Stability of ORS Formula and the Use of Trisodium Citrate(19)

Various trials in adults showed a significant decrease in the diarrheal stool output. However, the same benefit was not found in children. ORS citrate was as effective as ORS bicarbonate except that it had a longer shelf life. Despite this superiority in shelf life, the high cost restricts its use in developing countries where ORS bicarbonate is still being used.

Sodium Composition

Trials with low sodium(30, 32-34) have been found to be as effective as 90mmol/L (28,29,31). To decrease the possible risk of hypernatremia in newborns and young infants, various alternatives like 2:1 regimen (2 parts standard WHO ORS with one part of plain water or direct dilution) have been suggested(27,33). Whichever method is

TABLE I–*Electrolyte Content (mmol/L) of Stool Compared with Normal Plasma and Oral Fluid*

Condition	Na^+	K^+	CL^-	HCO^-_3
	mmol/L			
Cholera stools				
Adults	140	13	104	44
Children < 5 yrs	101	27	92	32
Enteritis stools				
Children < 5 yrs	56	25	55	14
Normal plasma	142	45	105	25
Oral fluid	90	20	80	30
				(111 glucose)

adopted, one thing is certain that additional plain water is essential to reduce the solute load. A point worth considering is that multiple commercial formulas with varying sodium content less than 90 mmol/L (standard WHO) are likely to cause inappropriate and erronous use in the hands of uninformed consumers–doctors and lay personnel.

Carbohydrate Composition

The recommended concentration of glucose is not more than 20 g/l *i.e.,* a 2% solution(35). Though initially 2.5 g was recommended, on further studies it was observed that best results were obtained with 20 g/l. Concentrations higher than that may lead to increased osmolar load. The glucose recommended may be either monohydrate or dihydrate. In situations where glucose is not available, and since it is expensive, sucrose in double the amount (40 g) is recommended instead of 20 g of glucose. Gur/jaggery/molasses have also been used as alternatives to sucrose. Glucose has been completely replaced in cereal–based(29,35,36) ORS with the principle that glucose is gradually released at the intestinal brush border from the cereal and this slow release has the advantage of enhancing sodium coupling mechanism without the disadvantage of increasing the osmolality. Further, cereals give additional calories to ORS.

Improved ORS Formula(19,20)

Because of the limitations of the glucose, salt based ORS and the need to feed the child during diarrhea and supply calories, much research has been undertaken to improve the formula. An improved (or Super ORS) formula, if successfully developed, should combine the benefits of oral rehydration with those of an antidiarrheal medication by enhancing the reabsorption of endogenous intestinal secretions and thus reducing the volume and duration of diarrhea. Two general approaches are suggested(19). The objective is to enhance the intestinal absorption of sodium and water by providing larger amounts of different types of organic carriers, than are present in the standard glucose based ORS.

In one approach, glucose (20 g/l) is replaced by a starch based cereal powder (50 g/l) or even larger amounts such as cooked rice powder(15,29,36). In the other approach, chemically defined ingredients such as glucose polymers (maltodextrin) or amino acids are either combined with or used in place of glucose in the ORS preparation(37,38). The advantage of using a starch like material is that during digestion, glucose is released slowly and promotes sodium absorption, as it does in glucose ORS(36). Because of its polymeric structure, however, relatively large amounts of starch can be given without causing ORS to become hyperosmolar. If these amounts of starch were given as glucose, the osmolality of the solution would be excessive and would cause an outpouring of fluid into the intestine which could worsen the diarrhea. In addition, aminoacids and small peptides liberated from the digestion of cereal proteins might further enhance sodium absorption. The use of synthetic aminoacids and dipeptides is based on evidence that these can promote the absorption of water and salt by mechanisms that are distinct from the mode of action of glucose. These results suggest that the use of synthetic aminoacids and dipeptides might provide an additional benefit when combined with glucose (or a polymer).

Cereal Based ORS

Recent studies in India(29,39), Egypt(40) and Bangladesh have confirmed the greater efficacy of rice based ORT reported earlier(15,36). In these studies undertaken in children aged 4 months to 10 years, the rate of stool output in the first 24 hours was reduced by 13 to 42%, total stool output by 15 to 49%, ORS intake by up to 31% and duration of diarrhea by 17 to 30%.

In the study by Mehta and Subramaniam(29), ORS containing rice (50 g) proved successful even in neonatal diarrhea. This was reassuring since doubts about its efficacy in this age group were raised as the pancreatic alpha amylase responsible for breakdown of starch polymers in the intestinal lumen is not fully well developed for the first 6 months of life. This finding may be attributed to the compensation by increased salivary amylase.

Further studies are underway to evaluate the safety and efficacy of rice-based ORS in severely malnourished children and in infants under 4 months of age. Though rice based ORS appears very promising it has its own drawbacks; it spoils easily in tropical climates and needs to be prepared at least twice a day. Therefore, studies have been initiated by WHO to determine whether an ORS that contains precooked rice could be made sufficiently stable to be used in a prepackaged form as the present glucose ORS.

ORS formulas based on other cereals such as sorghum, maize, wheat(41) and starches like sago(42) and potato have proved successful in some trials and are also currently being evaluated intensively.

Improved ORS Based on Defined Solutes

Glucose plus glycine (and Glycylglycine). Earlier studies(37,38) suggested that the addition of glycine to glucose ORS improved fluid absorption and reduced stool volume during acute diarrhea caused mostly by a toxigenic bacteria, *e.g., V. cholerae* 01, enterotoxigenic *E. coli*. One recent study(20) conducted in adults with severe cholera showed a 19% reduction in the stool output of the patients receiving the ORS that contained glucose and glycine, as compared with the output of the patients given standard ORS. Results from other studies(27,43,44) showed that the addition of glycine (and in some studies glycylglycine) to glucose ORS had no consistent beneficial effect on the rate of stool output, ORS intake, or duration of diarrhea in children under 3 years with acute diarrhea. Based on these results, it was concluded that although this approach might have some advantage in treating cholera and possibly diarrhea caused by other toxigenic bacteria, it was no more effective than standard ORS for infants and children with diarrhea of more diverse etiology(20).

ORS Containing Glucose Polymers (Maltodextrin) (20) and Amino Acids

By substituting maltodextrin for glucose in ORS solutions, it is possible to provide a source of glucose (in the form of medium-length polymers) equivalent in amount to that in standard ORS and to add an amino acid or dipeptide without the solutions becoming hyperosmoler. Several studies were promoted by WHO's Diarrheal Diseases Control Programme(43) and results from these studies suggest that an intermediate grade of maltodextrin plus glycine (and sometimes

glycyl-glycine), had no beneficial effect, in comparison with standard ORS.

ORS Containing Minimally Hydrolyzed Maltodextrin

The WHO has promoted several studies to evaluate an ORS containing 50 g per litre of a minimally hydrolyzed, more starch-like maltodextrin(44) in place of glucose. This maltodextrin is of particular interest for inclusion in ORS, because, in addition to being readily soluble and relatively inexpensive, it is stable when stored under tropical conditions. Studies of such an ORS formula are being done to determine whether this maltodextrin can enhance ORS efficacy to the same extent as rice-based ORS. Preliminary results from these studies(43,44), however, have revealed no appreciable benefit from ORS containing this type of maltodextrin in larger amounts.

L-Alanine Glucose ORS

Using experimental evidence that L-alanine is highly effective in transporting sodium across the intestinal brush border membrane, Patra and colleagues(45) recently conducted a study in adults and older children with cholera. Comparing a glucose and L-alanine ORS (16 g and 8 g per litre, respectively) with standard ORS, they demonstrated that the glucose and L-alanine solution is highly absorption efficient. Results indicated that the experimental ORS was associated with a 40% reduction in total stool output and a 26% reduction in ORS requirement. In addition, 40% of the patients treated with standard ORS required additional unscheduled intravenous therapy after starting oral rehydration, whereas only 4% of the patients receiving experimental ORS needed such therapy. Please note that the patients did not receive any antibiotic for 24 hours after starting treatment. These promising results led to further studies in young children under 3 years (India) with non cholera diarrhea and the results showed that this solution has no beneficial effect on stool output or duration of diarrhea.

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NOTES AND NEWS

PEDIATRIC AND NEONATAL EMERGENCIES
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