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EDITORIAL PERSPECTIVE

IMPROVED ORS FORMULATIONS

A quarter of a century ago (1964) Captain Robert Phillips demonstrated that a positive gut balance for sodium and water could be obtained over a short period using an orally administered glucose containing salt solution in a few actively purging cholera patients (1). Soon after, it was convincingly demonstrated that, in cholera patients, an optimally constituted oral rehydration fluid could replace massive losses due to acute secretory diarrhoea (2 – 6). Subsequently, a series of careful clinical trials and balance studies established its usefulness in infants and children with acute diarrhoea due to diverse aetiology (7 – 17). However, in 1968, after its first demonstration in cholera patients, for oral rehydration therapy (ORT) to be accepted globally, ORT is now recognised as a major scientific advance of practical importance, a powerful tool for the replacement of dehydration due to acute diarrhoea, an invaluable public health weapon, an essential component of primary care and a useful entry point for other child survival interventions. Appropriate feeding during and after diarrhoea is an essential part of optimal case management with ORT. The glucose – electrolyte solution recommended by WHO and UNICEF is prepared from a packaged mixture of glucose (20 g) and 3 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). This mixture (oral rehydration salts or ORS) is combined in one litre of water to prepare oral rehydration solution. The ORS formulation alone can rehydrate 90% of patients with dehydration; it can reduce the hospital admission rate for treatment of diarrhoea by at least 50% (18); reduce diarrhoeal mortality (19) and limit weight loss (20) when used with appropriate feeding. In addition, ORT using the present ORS formulation is one of the least expensive health interventions (21).

The limitations of the present ORS formulations

ORT with the present ORS formulations does not reduce the volume, frequency or the duration of diarrhoea (3,4,7,22). This raises the practical problem of its acceptance since a major concern of mothers and health workers during diarrhoea is to reduce the frequency and volume of the child's stools. This leads to a persistent desire to use antidiarrhoeal drugs. Research on antisecretory drugs for diarrhoea has so far been disappointing. Although global efforts have been successful in promoting ORT as part of many national diarrhoeal diseases control programmes, there has been, to date, little success in reducing the extensive and inappropriate use of antidiarrhoeal drugs that are either harmful or ineffective.

Basis of ORS formulations

As reported earlier (23,24), the absorption of a wide variety of organic solutes (e.g. d-hexoses, neutral amino acids, water soluble vitamins, etc.) by the small intestine is closely linked with the absorption of sodium (25). Of particular relevance to the development of an improved ORS formulation are a large number of *in vivo* intestinal perfusion studies conducted on animals and human volunteers (26 – 31). These studies provide information on the magnitude of the effect of various organic solutes on the absorption of sodium and water. It should, however, be noted that at the luminal concentrations attained by the organic solutes usually used in ORS formulations, salt absorption also takes place (*in vivo*) by an additional mechanism (27) called "solvent drag". This mechanism stated simply is as follows: as a result of the coupled sodium and organic solute entry process into the enterocyte and then into the circulation, water osmotically flows in the same direction; the bulk flow of water between and through the enterocytes traps additional sodium and chloride molecules in the flowing stream and increases salt absorption.

Three groups of organic solutes (mainly nutrients), such as, de-hexoses, neutral amino acids, and small peptides, are thought to be absorbed efficiently, and relatively independently of each other by the small intestine and enhance absorption of sodium and water.

Improved ORS formulations

It has been proposed (23,24) that absorption efficiency of an ORS formulation can be improved by exploiting a) organic nutrient-linked absorption, b) weak organic acid-linked absorption, c) osmotic and kinetic advantage of polymers, and d) colonic salvage of salts (sodium, potassium, and chloride) and water by short-chain fatty acids produced by fermentation of unabsorbed carbohydrates. Such an improved ORS formulation could not only successfully replace the deficit of salts and water in diarrhoea, but could also induce reabsorption of endogenous intestinal secretion and, thus, reduce the volume and duration of diarrhoea. In other words, it will then act as an absorption-promoting anti-diarrhoeal medicine. For our purpose we may define an improved ORS as one that: a) reduces stool volume by inducing reabsorption of endogenous secretion into the small intestine, b) shortens the duration or diarrhoea by reducing ileal effluent flow into the colon to less than its maximum absorptive capacity, c) reduces the failure rate of such therapy associated with high purging, and d) provides nutritional benefit by permitting early and effective feeding.

Osmotic forces in the gut lumen and ORS formulations

The major obstacle in designing an improved ORS is the osmotic force created by unabsorbed solutes within the gut lumen. Organic nutrients in ORS that are not absorbed create an adverse osmotic effect inside the gut lumen and reduce the efficiency of the solution. The rate of glucose absorption in acute diarrhoea has an upper limit and its higher concentration than that used in ORS formulations of glucose may lead to more frequent and severe malabsorption of glucose causing osmotic diarrhoea. It should be noted that when malabsorption of carbohydrate load leads to osmotic diarrhoea there is a relatively higher loss of water than of electrolytes and a consequent risk of hypernatraemia. It cannot be overemphasised absorption of the organic components is essential for the success of an improved ORS formulation. Possible ways to minimise adverse osmotic effects of an ORS formulation are: a) use of a combination of nutrients that do not compete with one another for absorption, e.g. d-hexoses, and neutral amino acids, and b) use of larger quantities of polymers of organic molecules, e.g. starches, glucose polymers, and proteins releasing glucose, small peptides and amino acids on digestion; adverse osmotic effect is less likely using this approach, because glucose and amino-acids are released slowly but absorbed rapidly.

Bicarbonate absorption and the salts of weak organic acids in the design of improved ORS formulations

Bicarbonate or citrate, included in ORS as sodium hydrogen carbonate or trisodium citrate, contributes to faster correction of the acidosis associated with diarrhoeal dehydration commonly seen in cholera. However, bicarbonate is actively absorbed from the small intestine against a steep electrochemical gradient and independently enhances sodium absorption (29,30) even when glucose-linked or amino acid-linked sodium absorption is maximised. This phenomenon, however, has not been studied in patients with diarrhoea. Weak organic acids, including short-chain fatty acids, like acetate, propionate and n-butyrate, are rapidly absorbed from both the small (32,33) and the large intestines (34) and enhance the absorption of sodium and potassium. This phenomenon is associated with bicarbonate secretion into the lumen. Sodium citrate (*in vitro*) has been shown to stimulate sodium and chloride absorption (35) by rabbit ileal mucosa both under basal conditions and during a secretory state induced by heat-stable enterotoxin (STa) of *Escherichia coli*. This effect on ion absorption was dose-dependent and the absorption of citrate was shown to be an active process.

Initially, standard ORS formulations included bicarbonate as the base. However, ORS containing sodium bicarbonate has problems of stability under the conditions of high humidity and heat found in many developing countries. Initial laboratory studies conducted by WHO demonstrated that ORS containing 2.9 g of trisodium citrate dihydrate in place of 2.5 g of sodium bicarbonate was the most stable of the formulations evaluated. Subsequently, nine clinical trials (36-41) were undertaken to compare the efficacy of ORS citrate and ORS bicarbonate (Table I); four of the nine studies were undertaken in adults and older children with cholera who presented with dehydration and acidosis. The acidosis was corrected by ORS citrate at a rate equal to that in patients receiving ORS bicarbonate.

TABLE I – SUMMARY FINDINGS OF SOME STUDIES OF CITRATE OR ACETATE – ORS COMPARED WITH CONTROLS GIVEN BICARBONATE – ORS

Study (Population)	Change in stool (%) 1st 24 h	Total	Change in ORS intake 1st 24 h	1st 24 h purging rate (ml/kg/h)
Islam R et al. (38) (adults, older children with cholera or ETEC)	– 38	–	0	3.3
Hoffman SL et al. (39) (adults, cholera)	– 27*	–	– 10	6.4
Majumder R et al. (41) (adults, cholera/ETEC)	– 18*	– 23	– 18	12.75
Patra FC et al. (64) (acetate – ORS in children)	– 17	– 22	0	7.1
Salazar – Lindo E et al. (40) (infants) +	0	–	0	7.1

* Change in stool output was statistically significant.
\+ Three other studies in infants promoted by WHO showed similar findings.
(Reference number in parenthesis)

In two studies in adults with cholera (39,41), the stool output was significantly less in those treated with ORS citrate, whereas in the other two studies (37,38), there was a similar trend. In five studies undertaken in children (36,40) aged under three years with moderate – to – severe dehydration resulting from non – cholera diarrhoea, the ORS citrate was found to be uniformly as effective as ORS bicarbonate in correcting acidosis. However, there was no reduction of stool output in children treated with ORS citrate. One may speculate that citrate in ORS improves its absorption efficiency in high output secretory diarrhoea due to cholera.

Clinical studies with improved ORS formulations

In 1984, encouraged by the promising results from a few clinical trials, the Diarrhoeal Diseases Control Programme of WHO began supporting research projects to develop improved ORS formulations. In addition, several investigators around the globe began independent evaluations of improved ORS formulations. Such solutions, if successfully developed, would combine the benefits of oral rehydration with those of an antidiarrhoeal medicine.

Two general approaches towards such solutions have been studied. In both, the objective is to enhance the intestinal absorption of sodium and water by providing larger amounts of different types of organic carriers. In one approach, glucose (20 g/l) is replaced by a cereal powder (e.g. 50 g/l), such as cooked rice powder. Alternatively, chemically defined ingredients, such as glucose polymers (e.g. maltodextrin) or amino acids, are either combined with or used in place of glucose in the ORS preparation.

The advantage of using a starch – containing cereal powder is that glucose is slowly released from starch during digestion promoting sodium absorption as in glucose – ORS. However, because of its polymeric structure relatively large amounts of starch can be given without causing ORS to become hyperosmolar. If these amounts were given as glucose, the osmolality of the solution would be excessive and cause an outpouring of fluid into the intestine which could worsen diarrhoea. In addition, amino acids and small peptides liberated from digestion of cereal proteins may further enhance sodium absorption.

The use of synthetic amino acids and peptides is based on evidence (42 – 51,23) that these can promote water and salt ab –

sorption by mechanisms that are distinct from that of glucose. This suggests that they may provide an additional benefit when combined with glucose (or a polymer of glucose).

Improved ORS based on defined solutes

Glucose plus glycine and glycyl-glycine (Table II)

Earlier studies were conducted on the addition of glycine to glucose ORS by Nalin and colleagues (52) at ICDDR,B, Dhaka and later by Patra and colleagues (53) in Calcutta. Results of these studies suggested that this addition improved fluid absorption and reduced stool volume during acute diarrhoea caused mostly by toxigenic bacteria, e.g. *V. cholerae* O1, enterotoxigenic *E. coli* (ETEC). Glycyl-glycine was considered as a substrate because of experimental evidence (43) that it enhances sodium absorption by a mechanism apparently independent of that of glycine. Five studies (promoted by WHO) evaluating ORS solutions containing glycine (in some cases combined with glycyl-glycine), in addition to glucose have been completed (54). In two studies [Costa Rica (55) and Peru (54)], the concentration of glucose was reduced to 12 g per litre to avoid hyperosmolality. One of these studies conducted in adults with severe cholera (Moechtar *et al.* - personal communication) showed a 19% reduction in stool output in patients receiving the ORS containing glucose and glycine as compared with those given standard ORS. However, results from the remaining four studies showed that the addition of glycine, and in some studies glycyl-glycine, to glucose ORS had no consistent beneficial effect on the rate of stool output, ORS intake or duration of diarrhoea in children aged under three years with acute diarrhoea [Costa Rica (55), Peru (54), Philippines (56)]. Based on these results, it was concluded that although this approach may have some advantage in treating cholera and possibly diarrhoea caused by other toxigenic bacteria, it was no more effective than standard ORS for patients with diarrhoea of more diverse aetiology, particularly in infants.

ORS containing glucose polymers (maltodextrin) and amino acids (Table II)

By substituting maltodextrin for glucose in ORS solutions it is possible to provide a source of glucose (in the form of medium chain length polymers) equivalent in amount to that in standard ORS and to add an amino acid or dipeptide without the solutions becoming hyperosmolar. Several studies were promoted (Burma, Egypt, India, Nigeria, Venezuela) by the Diarrhoeal Diseases Control Programme of WHO (54) 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 hydrolysed maltodextrin (Table II)

Several studies have been promoted by WHO to evaluate an ORS containing 50 g per litre of a minimally hydrolysed more starch like maltodextrin (56) 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 formulation are seeking to determine whether this maltodextrin can enhance ORS efficacy to the same extent as rice-based ORS. Preliminary results from these studies [Bangladesh, Egypt, India, Philippines (54,56)] have, however, revealed no appreciable benefit from ORS containing this type of maltodextrin in larger amounts. The results elude explanation as to why such a glucose polymer should not act like rice starch.

Amino acid L-alanine and glucose-ORS (Table II)

Based on experimental evidence that L-alanine is highly effective in transporting sodium across the intestinal brush border membrane (57), a study was recently conducted by Patra and colleagues (58) at ICDDR,B in adults and older children with cholera using a glucose and L-alanine based ORS (16 g glucose and 8 g L-alanine/l) compared with standard ORS. They demonstrated that such a solution is highly absorption efficient; the results indicated that experimental ORS was associated with a 40% reduction in total stool output and a 26% reduction in ORS requirement. In addition 40% in the group treated with standard ORS required additional unscheduled intravenous therapy after starting oral rehydration, whereas only 4% needed it in the group receiving experimental ORS. It should be noted that the patients did not receive any antibiotics for

TABLE II – ORS BASED ON DEFINED SOLUTES: CHANGES IN STOOL OUTPUT, ORS INTAKE AND DIARRHOEA DURATION AS COMPARED WITH CONTROLS GIVEN ORS

Study (Population)	Change in stool output (%)		Change in ORS intake (%)		Change in diarrhoea duration	1st 24 h purging rate in controls (ml/kg/h)
	1st 24 h	Total	1st 24 h	Total		
Glycine + Glucose						
Nalin D et al. (52) (adult cholera)	–	–39	–	–	–24	10.2
Patra FC et al. (15) (children, includes cholera)	–36	–49	–	–30	–30	11.5
Salazar L et al. (54) (infants, reduced amount of glucose)	0	–7	–4	–	–	–
Santosham M et al. (77) (infants, 36% rotavirus diarrhoea)	+26	+13	+13	–	–3	2.7
Vesikari T et al. (76) (children, mainly rotavirus diarrhoea)	+16	–	–	–	–	1.5
Other compositions						
Pizarro D et al. (55) (infants, glucose 67, glycine 53, glycyl–glycine 30 mmol/l)	0	–	0	–	–	–
Roemer H et al. (54) (infants, maltodextrin 50 g/l)	+20	+14	+ 9	–	–	–
Patra FC et al. (58) (adults with cholera or ETEC, L–alanine 8 g + glucose 16 g/l)	–39	–44	–18	–	–15	13

(Reference number in parenthesis)

24 hours after starting treatment. However, initial results from studies in children aged under 3 years (India) with non–cholera diarrhoea (56) showed that this solution has no beneficial effect on stool output or duration of diarrhoea.

Amino Acid L–glutamine and gucose–ORS

A recent *in vitro* study (Rhoads MK – personal communication) demonstrated that L–glutamine when used with glucose stimulates metabolism of intestinal epithelial cells and transport of sodium; in addition, it uniquely stimulates electroneutral NaCl absorption across the normal and rotavirus–damaged pig intestine. In light of these findings, two clinical trials to evaluate the efficacy in young children of ORS containing L–glutamine and glucose as substrates have been initiated with support from WHO. A recently completed marker perfusion study at ICDDR,B with L–glutamine containing solutions in actively purging cholera patients showed that

L-glutamine is highly efficient in stimulating sodium absorption from the small intestine (Van Loon FP *et al* - personal communication).

Cereal-based ORS

Polysaccharides from cereals and legumes (mainly amylopectin and amylose) are hydrolysed by pancreatic and salivary amylases into short-chain glucose polymers. These polymers, in turn, are hydrolysed by mucosal glucosidases into glucose for absorption (59). Deficiency of pancreatic amylase in infants aged under 6 months may be compensated for by salivary amylases and possibly mammary amylases in breast-fed infants. Based on breath hydrogen tests, it has been shown (60,61) that nearly all healthy adult subjects fail to absorb a portion of dietary starch (an estimated 6 to 20%) eaten in the form of common foods made from corn, potato, oats, and wheat with the exception of rice starch (100% of which was absorbed). However, malabsorbed carbohydrate is degraded by colonic bacteria to produce short-chain fatty acids, hydrogen and other products. In an elegant study by Shulman and colleagues (62), it was demonstrated that healthy 4-week old infants given a dose of 3 g/kg/day of corn starch partially digested it in the small intestine and largely salvaged the rest of it through colonic fermentation and absorption of short-chain fatty acids; the extent of use of cereal starch was comparable to that with glucose or a glucose polymer. Young infants digest, albeit incompletely, and absorb starch from cereals in the small intestine, while a colonic salvage mechanism recovers much of the malabsorbed carbohydrate.

Studies in human volunteers (45) have shown that meal protein is digested 60% in the upper small intestine and 40% in the distal small intestine, and the ileum actively takes part in protein digestion and absorption. Protein digestion and absorption are efficient even in malnourished children. The brush border membrane of the intestinal mucosa is efficient in the hydrolysis of peptides with 3 to 6 amino acid residues.

Rice-based ORS studies (Table III)

In 1982, Molla and his colleagues (63) demonstrated that a rice powder-based ORS (30 g/l) was as effective as sucrose-based ORS (40 g/l) in adults and older children with cholera. In the same year, Patra and his colleagues (64) reported a randomised controlled trial in children aged under 5 years in which a rice-based ORS using a higher quantity of rice powder (50 g/l) could significantly reduce the volume (by 49%) and the duration (by 30%) of diarrhoea. In a subsequent randomised trial in adults and older children with predominantly cholera, Molla and colleagues (65) used a larger amount of rice powder (80 g/l) in a ORS formulation and confirmed that ORS based on a large quantity of rice powder is substantially more absorption-efficient than glucose-ORS (reducing diarrhoeal stool by 28% and ORS consumption by 27%). In a subsequent study, Patra and his colleagues (66) conducted a controlled clinical trial using an ORS based on 50 g of rice powder plus an amino acid, glycine (8 g/l), and showed that adding a neutral amino acid to rice powder does not further improve its absorption efficiency. Two other studies, conducted in infants and small children in India and Egypt (67,68), used 50 g/l of rice powder-based ORS. The study in India demonstrated only marginally improved absorption efficiency of rice powder-ORS compared with glucose-ORS, whereas the one in Egypt demonstrated a marked degree of absorption efficiency for rice-ORS.

Two recent studies in Kenya (69) and Bangladesh (70) also tested rice-ORS along with several other cereal powder-based ORS formulations. The study in Kenya did not show any improvement with rice-ORS compared to glucose ORS, whereas the study of Molla and colleagues in children with predominantly cholera or enterotoxigenic *E. coli* diarrhoea demonstrated that rice-ORS reduced the stool output by as much as 53% during the first 24 hours of treatment. Recently, 3 additional clinical trials with rice-ORS (50 g/l) have been reported in infants and small children: one from Egypt (Santosham *et al.* personal communication) and two from India (71,72). In all three, there was a trend towards a reduced stool output (13-20% in first 24 hours) which did not achieve statistical significance. We attempted to relate the demonstrated absorption efficiency of rice-ORS formulations with the purging rate (Table 3), and it appears that the studies which demonstrated rice-ORS to be highly absorption-efficient were conducted in patients whose purging rate was high. Those studies which showed either no improvement or marginal improvement in diarrhoea stool output were conducted in infants and children

TABLE III – CHANGES IN STOOL OUTPUT AND ORS INTAKE IN CHILDREN WITH ACUTE DIARRHOEA TREATED WITH RICE-ORS (50 G/L) FORMULATIONS AS COMPARED WITH CONTROLS GIVEN ORS: RELATION WITH PURGING RATE

Experiment	Change in stool output (%)		Change in ORS intake (%)	Change in diarrhoea duration	1st 24 h purging rate (ml/kg/h) in control groups
	1st 24 h	Total	1st 24 h		
1. Molla AM et al. (70)	-53	-	-28	-	14
2. Alam AN et al. (78)	-55	-	-10	-	12
3. Patra FC et al. (16)	-42	-49	-31	-30	7
4. Patra FC et al. (66) (50 g rice+8 g glycine/l)	-35	-41	-32	-11	7.5
5. El Mougi M et al. (68)	-33	-	-21	-17	10.2
6. Mohan M et al. (72)	-20	-	-16	-	4.59
7. Dutta P et al. (71)	-17	-21	-07	-12	4.3
8. Bhan MK et al. (67)	-13	-	+2.5	-	3.2
9. Kenya PR et al. (69)	-03	-	-08	-09	4.3

1,2 – Predominantly older children with cholera.
3,4,7 – Children up to age 5 years including some patients with cholera.
5,6,8,9 – Infants and small children; does not include cholera patients.
(Reference number in parenthesis)

whose purging rates were low.

Studies are underway to evaluate the safety and efficacy of rice-based ORS in severely malnourished children and in infants aged under 4 months. Results are not yet available. The preparation of rice powder is time-consuming and requires fuel. Thus studies have been initiated to determine whether an ORS that contains precooked rice could be made sufficiently stable to be used in a prepackaged form, like the present glucose-ORS. Two varieties of industrially produced precooked rice preparations have undergone stability tests using simulated tropical storage conditions and they have been found to be highly stable and comparable with glucose-ORS when packaged in aluminium foils (WHO – unpublished). Clinical trials using precooked rice-based ORS are underway in adults with cholera and in infants and children with non-cholera diarrhoea. Preliminary results of a study in cholera patients (Moechtar *et al.*) demonstrated (56) that this stable packaged ORS is highly absorption-efficient (reducing diarrhoea stool output by 30% and ORS intake by 31%). Results of stability tests suggest that it may be feasible to use precooked rice powder as a component of packaged ORS.

Effect of a diet containing cooked rice on efficacy of glucose-ORS

Can the efficacy of rice-ORS be equaled by giving glucose-ORS and a diet containing cooked rice? Rice-ORS would have little practical advantage if comparable benefits could be achieved by early feeding of patients given glucose-ORS because early feeding as such is an essential component of optimal case management. A recent review by WHO (73) examined studies with rice-ORS in which the study design included early feeding with rice-based diet (255 subjects mostly with cholera) or rice-based formula (136 children with non-cholera diarrhoea); it

was concluded that rice-ORS retains its advantage over glucose-ORS and the magnitude of the benefit is similar to that seen in patients who were fasted or given a diluted formula during the first 24 hours of ORT. In a randomised trial in Burma (74), the impact of feeding boiled rice on glucose-ORS efficacy was evaluated in children with cholera. Children in the study group were fed boiled rice from the start along with ORT and the controls were starved for 24 hours. The group fed boiled rice plus glucose-ORS had significantly higher purging rate but had better weight gain on completion of treatment compared to controls receiving glucose-ORS and who fasted for 24 hours. Recently, in a randomised 4-cell clinical trial at ICDDR,B (Alam N *et al.* personal communication) in adults with cholera early liberal feeding with a rice-based diet did not improve the efficacy of glucose-ORS or rice-ORS. The magnitude of difference in the first 24 hours and total stool output between patients receiving rice-ORS and those receiving glucose-ORS remained closely similar irrespective of whether they were starved for 24 hours or fed with rice meals. Observations suggest that a rice diet does not make glucose-ORS as absorption efficient as rice-ORS.

Studies of ORS formulations based on other cereals

Two clinical trials, using ORS formulations based on cereals other than rice, have recently been reported; one from ICDDR,B (70) used ORS formulations based on rice, maize, sorghum, millet, wheat, or potato and compared them with standard glucose-ORS in children with acute diarrhoea mainly due to *V. cholerae* or ETEC. The other study reported from Kenya (69) also used ORS formulations based on maize, sorghum, rice, or millet and compared them with glucose-ORS in infants and children with diarrhoea from an area where cholera is not endemic. The study at ICDDR,B demonstrated that ORS based on other foods, i.e. maize or sorgum or wheat or potato or millet were all highly absorption-efficient compared to glucose-ORS, rice-ORS being the most efficient. However, the study in Kenya demonstrated that ORS based on maize or sorgum, millet, or even rice was as absorption-efficient as glucose-ORS but not superior. As suggested earlier, one explanation for this negative result is that the study was conducted in infants and children with a low purging rate (4.3 ml/kg/h compared to the children studied at ICDDR,B in whom the mean purging rate was as high as 14 ml/kg/h).

A field evaluation of packaged rice-ORS

A field study has recently been completed (75) with a rice-based ORS at ICDDR,B. Some of the findings of this study, if confirmed, have implications for global diarrhoeal diseases control programme. The study was conducted in three communities in Chandpur near Matlab field station of ICDDR,B by Bari and his colleagues. Packets of partially cooked rice-ORS and standard glucose-ORS were made available in two communities, respectively. A third community receiving no ORS formulation acted as a control. All the mothers of 0-4-year old children in these two intervention cells were trained to prepare and use the respective types of ORS. A selected number of mothers were depot holders and distributors of ORS for their community. The third community, used for comparison, was advised to use locally available treatment facilities provided by village practitioners. The overall impact of these interventions on diarrhoeal morbidity and outcome in the communities were observed for two years through surveillance and follow-up of diarrhoeal episodes. Results of the study showed that the failure rate (as defined by hospitalisation or death) was significantly less in the community provided with rice-ORS (1.2 vs 5.5 per 1000 episodes). Mean duration of diarrhoea was significantly less (3.3 vs 5.5 days; median duration of diarrhoea was 3 and 5 days respectively). Although further in depth analysis of the data is required with particular reference to the comparability of the two groups of children as to their nutritional status and other important confounding variables, these results have important implications for prevention of prolonged diarrhoea and for policies on early home therapy. Therefore, further studies have now been initiated at ICDDR,B to confirm these findings.

What have we learned from clinical trials of rice-ORS?

These studies suggest that:

i) Stool output during the first 24 hours of treatment is significantly reduced in patients with acute diarrhoea given rice-based ORS (containing 50-80 g per litre

of cooked rice) as compared with patients given the standard glucose-ORS, the effect being substantially greater in severely purging patients than in less severe non-cholera diarrhoea;

ii) treatment with rice-based ORS also reduces the duration of diarrhoea;

iii) the combined effect of a reduced rate of stool loss and the duration of diarrhoea leads to even greater per cent reduction in total stool output till cessation of diarrhoea;

iv) the effect of rice-based ORS on total stool output in acute non-cholera diarrhoea in small children has not been precisely defined and deserves further study; and

v) feeding a rice-based diet to patients given the standard ORS does not reduce stool output as much as treatment with rice-based ORS.

Research recommendations on rice-based (and other cereal-based) ORS may include:

i) the relative benefit of rice-ORS should be more accurately determined in young children with non-cholera diarrhoea to develop recommendations on the possible use of rice-ORS to treat such patients when seen at health facilities; such studies should measure the duration of diarrhoea and stool output, and the study design should include early feeding with rice and other foods;

ii) evaluate the safety and efficacy of rice-ORS in infants aged under 4 months and in severely malnourished children with acute diarrhoea;

iii) determine whether the acceptance of rice-ORS and its correct use in the home, e.g. in patients seen at a treatment centre and sent home with ORS, is better than glucose-ORS, particularly when rice-ORS is promoted as an antidiarrhoeal medicine in addition to being a hydrating fluid;

iv) conduct community-based studies to evaluate the role of cereal-based ORT in shortening the duration of diarrhoea, reducing the rate of persistent diarrhoea, and rendering nutritional benefit; and

v) evaluate the feasibility and cost of producing a stable, packaged, ready-to-use rice-ORS in developing countries as an option to standard glucose-ORS.

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