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ORGANIC SUBSTRATE AND ELECTROLYTE SOLUTIONS FOR ORAL REHYDRATION IN DIARRHEA

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INTRODUCTION

Glucose-Oral Rehydration Solution (G-ORS): An Effective Treatment of Dehydration

G-ORS has produced such positive results in dehydrated patients that no further scientific demonstration is needed to confirm its efficacy. G-ORS is usually prepared by mixing salts (sodium chloride, sodium citrate, and potassium chloride) and glucose contained in a sachet in one liter of plain water (Table 1). When an appropriate amount is given orally to a child or adult with signs of dehydration resulting from acute watery diarrhea, it rehydrates the patient within 4–8 h (55, 143).

The composition of G-ORS is directly based on the pathophysiological characteristics of diarrhea, which is defined as a loss of water and electrolytes in stools (54). The electrolyte composition of G-ORS resembles that of watery stools (102, 103) (Table 2). Glucose is added to stimulate intestinal absorption of NaCl, which in turn stimulates water absorption (105). Consequently, G-ORS can be expected to actively induce rehydration in any clinical situation in which intestinal absorption of glucose and NaCl persists (122).

Explicit in its name, G-ORS is effective orally. In the 1950s, considerable effort was made to develop a solution that could rehydrate. Initially, the i.v. route was chosen, probably because of the ineffectiveness of available solution by the oral route and improvements in medical equipment (sterile apyrogene solutions and tubings, fine needles, etc) and in the training of the medical staff. Thereafter, in the late 1960s, when efficacy of G-ORS by the oral route was demonstrated, G-ORS administration via this route was immediately envisaged for use outside specialized centers in primary health care facilities, where dehydrated patients first present for consultation (67, 127).

Table 1 Recommended composition of an oral rehydration solution

Composition in mmol/L	WHO[a]	AAP[b]	ESPGAN[c]
sodium	90	75–90	60
potassium	20	20	20
citrate	30	20–30	10
chloride	80	70–80	70
glucose	110	110–140	74–111

[a] World Health Organization
[b] American Academy of Pediatrics
[c] European Society of Pediatric Gastroenterology and Nutrition

Table 2 Electrolyte composition of diarrheal stools (means expressed in mmol/liter)

	Normal adult[a]	Stool children[b]	Cholera adult[c]	Cholera children[d]	ETC[e] adult	ETC[e] children[d]	Rotavirus children[d]
Na^+	31	46	133	88	97	53	37
K^+	75	91	20	30	30	37	38
Cl^-	16		100	86	66	24	22
HCO_3^-	40		41	32	37	18	6

[a] Data from Ref. 70b.
[b] Data from Ref. 126b.
[c] Data from Ref. 112b.
[d] Data from Ref. 85.
[e] Enterotoxigeric *Escherichia coli*

In this regard, one of the first steps undertaken by the World Health Organization (WHO) to promote the implementation of the global program was a rational evaluation of the potential need for G-ORS in all regions where diarrhea was a major health problem. The results, published in 1982 in the now famous paper by Snyder & Merson, were surprising in that they indicated that in children under 5 years of age, 5 million of 1000 million episodes of diarrhea resulted in death annually (135).

Obviously, all of these children did not enjoy optimal nutritional status, and malnutrition was already recognized as a major contributing cause of death. Because diarrhea was considered a factor of malnutrition, it was thought that G-ORS would help reduce malnutrition and thereby lower the number of deaths among children under five years of age (57).

Why Should Other Organic Substrates Be Considered as Alternatives to Glucose?

The growing use of G-ORS in most countries confirmed its efficacy in rehydrating patients with acute dehydration. At the same time, however, its limitations also became apparent. Its diversity of application led to several problems as a result of (*a*) its use in various settings by many types of physicians and nonphysicians, (*b*) the different etiologies of diarrhea, and (*c*) differences in patients' age and nutritional, socioeconomic, and cultural status.

G-ORS use has four primary limitations. First, acute diarrhea is in itself a paradox because it is both a benign disease and one of the main causes of mortality among young children. Indeed, diarrhea is so common in children that mothers—and frequently doctors—do not identify it as a disease requiring specific medical treatment, and most cases do recover without treatment (36). The estimated percentage of episodes of diarrhea associated with clinical signs of dehydration is ~ 5%, and the number of resulting deaths is estimated at ~ 0.5%. The use of G-ORS was therefore extended to prevent dehydration

and as such was recommended for use in primary health care centers and even at home for what is known as home fluid therapy (69, 72, 144). Thus, the apparent contradiction between the message of diarrhea as a life-threatening disease and the familial observation of diarrhea as a self-limited disease did not help in the use of a common treatment for both conditions (36).

Second, although G-ORS is an effective treatment for diarrhea, it does not reduce the symptoms of diarrhea. When given in excess, it may even increase the volume of watery stools (26, 42b, 123). Therefore, G-ORS did not meet the expectations of families seeking symptomatic treatment of diarrhea for children without clinical signs of dehydration, which is by far the most frequent clinical situation.

Third, it soon became obvious that the G-ORS sachets were not available to all families or even to all primary health care centers. Thus locally available alternative substrates with physiological properties equivalent to those of glucose were needed.

Lastly, the beneficial effect of G-ORS on nutritional status has been questioned (21). By itself, 20 g of glucose per liter of ORS did not constitute a significant source of energy. WHO therefore recommended the use of both G-ORS for rehydration and maintenance of hydration together with early feeding in order to minimize the adverse nutritional consequences of diarrhea (144).

In summary, the main directives that prompted the search for alternative substrates to glucose in ORS were (*a*) to reduce the symptoms of diarrhea, (*b*) to increase the local availability of ORS while preserving or strengthening its effect on rehydration, and (*c*) to enhance the nutritional value of the treatment of diarrhea.

Is the Electrolyte Composition of the G-ORS Optimal for Rehydration?

The mechanism of dehydration relating to acute diarrhea is best explained by the enterosystemic cycle of water, in which the balance between the secretion and absorption of water and electrolytes is considered a dynamic process (Figure 1; 37, 38). In this context, diarrhea can be defined as an increase in water and electrolytes in stools as a result of an imbalance between absorption and secretion. This imbalance may represent either a relative increase in secretion compared with absorption or a relative decrease in absorption compared with secretion. These processes may also coexist simultaneously.

Therefore, the composition of rehydration solutions designed to replace stool losses was generally based on that of diarrheal stools (Table 2). In developing countries, the reference was cholera, whereas in North American and European countries, it was rotavirus infection (115).

The first part of this review focuses on the physiological reasons for selecting alternative organic substrates and defines optimal electrolyte composition. In

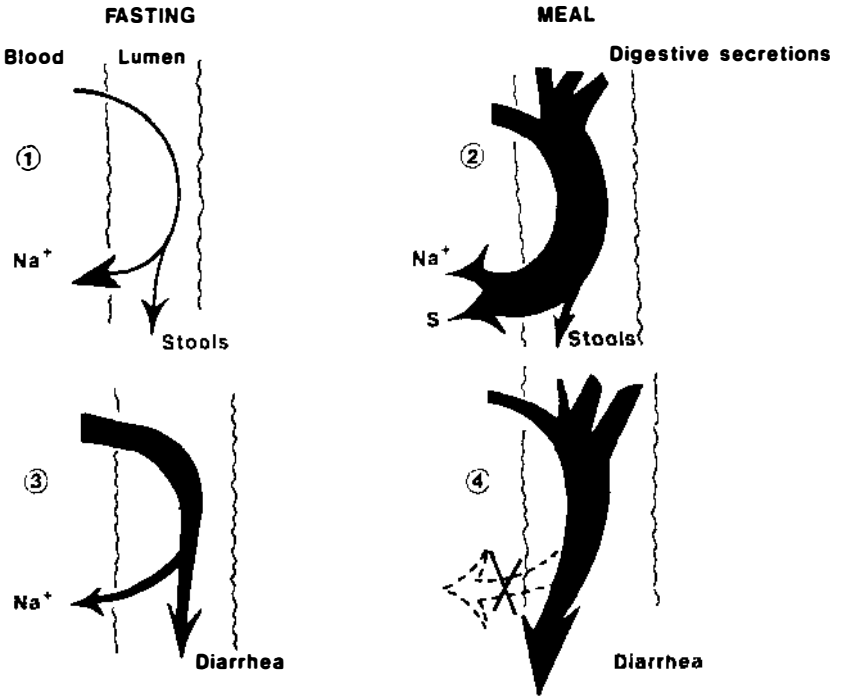

Figure 1 The enterosystemic water cycle. (Panel 1). During fasting, water that enters the lumen is reabsorbed following Na^+ absorption from lumen to blood (141). Therefore, very little water is lost in stools. (Panel 2). During a meal, large amounts of water enter the intestinal lumen as a result of digestive secretions (saliva, gastric, biliopancreatic, intestinal). Water is reabsorbed following Na^+ reab- sorption, mainly through the solute-Na^+ cotransport systems. Again, little water is lost in stools. In this system, diarrhea is a consequence of imbalance between absorption and secretion resulting from either increased secretion (Panel 3) or decreased reabsorption (Panel 4).

the second section, the main results obtained during clinical trials with various ORS are critically analyzed. The third part of the review discusses possible ways to improve ORS. Although the treatment of dehydrated patients is based on physiological considerations, it may not be fully effective if certain economic (133) and social factors that have recently been analyzed (36) are not also taken into account.

SUBSTRATES CHOSEN ON THE BASIS OF PHYSIOLOGICAL CONSIDERATIONS

The choice of substrates was based on straightforward considerations. The small intestine is the site through which the largest amounts of water and

electrolytes are transported daily (39); it is also the site of organic substrate absorption. In addition, at the cellular level, the absorption from lumen to blood of substrates that are candidates for ORS is a two-step process: At the luminal membrane, these substrates are cotransported together with Na^+, but when crossing the basolateral membrane, they leave the enterocyte via a Na^+-independent process (145). Consequently, Na^+ absorption is stimulated by the presence of the substrate at the luminal membrane. The stimulatory effect of the substrate is directly related to its molecular structure and not to the surplus energy it may supply through its metabolism. For example, glucose does not stimulate Na^+ absorption by supplying a surplus of ATP to the Na^+-K^+ ATPase on the basolateral side of the enterocytes (49), but rather by binding to the cotransporter present on the luminal membrane. Although most water-soluble substrates are probably cotransported with Na^+, only monosaccharides, amino acids, and di- or tripeptides are present in the intestinal lumen in sufficient amounts to stimulate Na^+ absorption via a cotransport mechanism. Of the monosaccharides, both glucose and galactose—but not fructose—stimulate Na^+ absorption, and amino acids and some dipeptides are also directly coupled to Na^+ absorption. The efficacy of amino acids in stimulating Na^+ absorption depends on the nature of these amino acids. The basic or cationic amino acids are poor stimulators of Na^+ absorption, and acidic amino acids stimulate it more than neutral amino acids. Neutral amino acids stimulate Na^+ absorption as effectively as glucose (31, 132). Among the dimer or small polymer molecules, carbohydrates such as sucrose or maltodextrins are first hydrolyzed to glucose molecules, whereas small peptides can stimulate Na^+ absorption either without hydrolysis or after hydrolysis into amino acids (5).

The choice of the concentration of the substrate candidate was essentially based on the osmolality of the solution. Physiological studies clearly showed that the small intestine is a leaky epithelium that cannot absorb water and electrolytes against a steep osmotic gradient between lumen and blood. The upper limit of osmolality at which intestinal absorption is reduced to zero is ~ 400 mOsm/liter in the lumen compared with 300 mOsm/liter in the blood (32, 142). Therefore, the choice of substrate concentration was designed to reach a final osmolality of $\leq$ 300 mOsm/liter of ORS.

These physiological considerations were justified by the finding that many traditional solutions used to treat diarrhea (e.g. rice-water) have a low osmolality (frequently $\leq$ 150 mOsm/liter) (56). Moreover, clinical evidence indicates that raising the glucose concentration above 20 g/liter increases stool volume (D Mahalanabis, personal communication). The reasons for the choice of organic substrates in ORS are summarized in Table 3.

Table 3 Organic substrates: candidates for use in ORS

Chemically defined	Main reason	Secondary reason
Carbohydrate		
Glucose	Na^+ absorption	
Sucrose	availability	Na^+ absorption
Glucose polymers (maltodextrins)	low osmolarity	Na^+ absorption
Amino acids		
Glycine	low cost	Na^+ absorption
Alanine	Na^+ absorption	
Glutamine	Metabolism	Na^+ absorption
Dipeptides		
Glycyl glycine	Na^+ absorption	
Locally available food		
Cereals		
Rice	Availability and	Na^+ absorption,
Maize	low cost	low osmolarity
Millet	"	"
Sorghum	"	"
Wheat	"	"
Green gram	"	"
Fruit		
Plantain	"	"
Tubers		
Potatoes	"	"

CRITICAL EVALUATION OF THE RESULTS OBTAINED WITH DIFFERENT SUBSTRATE-ORS

Presentation of the Results

CHEMICALLY DEFINED ORGANIC SUBSTRATES **Glucose remains the reference substrate for ORS (24, 76, 89, 104, 106). It is effective at the concentration of 110 mmol/liter. Replacement of glucose with sucrose, which supplies an equal amount of glucose, yields an ORS as effective as standard G-ORS (26, 87, 98, 123, 124). Hence in those parts of the world where glucose is an imported commodity, sucrose can be substituted. Replacement of glucose by brown**

sugar molasses also does not hamper the rehydration efficacy of ORS (60, 61). However, no additional clinical advantages were found when maltodextrins, amino acids, or dipeptides were used instead of glucose (6, 16, 17, 90, 95, 100, 101, 110, 119, 128, 137).

LOCALLY AVAILABLE FOOD As already pointed out, the standard prepackaged glucose-based ORS, which has an excellent rehydrating capacity, fails to meet the main expectation of mothers and many health-care workers: cessation of the diarrhea. Failure to reduce stool output often leads to the use of antidiarrheal medicines and antibiotics that may contribute to the development of persistent diarrhea and malnutrition (74). To increase the universal acceptance, availability, and food-like character of ORS, cereals were included in its composition as a source of glucose. Various cereals have been tested as ORS substrates, including rice, maize, millet, and sorghum wheat (4, 11, 14, 15, 42b, 50, 64–66, 68, 70, 80, 82–84, 99, 111). Cereal-based ORS (C-ORS) are as safe and effective as G-ORS in rehydrating children with diarrhea of diverse origins (48), even in cases of severe malnutrition (114).

RESULTS FOR ELECTROLYTES Initial studies of the effects of rehydration solutions used Na^+ concentrations of 100–133 mmol Na^+/liter. These solutions proved to be effective rehydration agents in cholera diarrhea (55). Later, a solution for universal use containing 90 mmol Na^+/liter also induced effective rehydration at all ages in patients with diarrhea caused by a variety of etiological agents, from cholera to *Escherichia coli* and rotaviral infections (1, 4, 16, 59, 60, 84, 93, 98–101, 108, 123, 126). Failure rates varied from 0–20%, but the highest rates occurred only in cases of cholera.

Fear of hypernatremia in noncholera diarrheal dehydration prompted comparison of different solutions containing 40, 50, 60, or 75 mmol Na^+/liter, with a reference solution containing 90 mmol Na^+/liter (7, 28, 30, 33, 42a, 53, 63, 81, 91, 107, 121, 129). In general, no clinical differences in the effectiveness of rehydration were noted. Among patients receiving the lower Na^+ oral solutions, some cases of hyponatremia were reported, and hypernatremia occurred in a small percentage of those receiving the 90 mmol Na^+/liter solutions. For the most part, however, no clinical signs of mineral disturbances were observed. Failure rates were low, at 0–7%. Comparison of i.v. and oral rehydration showed that the two routes were equally effective (73, 136, 138), although less rehydration solution was generally needed with i.v. rehydration.

The addition to ORS of plain water in a ratio of two volumes of ORS to one volume of water was as effective as ORS without water (91, 92, 109, 112). This result was observed in a wide range of patients of different ages presenting with hyper- or hyponatremic dehydration, including neonates.

In different studies, hypokalemia was observed in 12–30% of dehydrated

patients. When K^+ was not added to the ORS, the initial hypokalemia persisted. Even when the ORS contained 10 mmol/liter K^+, hypokalemia still persisted in as many as 20% of the patients, and with 20 mmol/liter K^+, as many as 30% of patients developed hypokalemia during the rehydration in several studies. However, when 30–35 mmol/liter K^+ was added to the ORS, hypokalemia neither developed nor persisted (2, 30, 58, 91).

In severe choleraic dehydration, bicarbonate losses were 48 mmol/liter. In some patients, the addition of 48 mmol/liter bicarbonate to ORS caused hypocalcemia and tetany (88). However, because such bicarbonate addition may result in brownish coloration of rehydration solutions in tropical climates, citrate was used as an alternative and proved equally effective. Solutions without citrate or bicarbonate restored metabolic acidosis more slowly, over a period of more than 24 h. In some series, lower citrate solutions (10 mmol/liter) led to slower recovery of acidosis. A concentration of 30 mmol/liter of citrate in bicarbonate was effective in correcting metabolic acidosis (1, 33, 58, 62, 125); however, in addition to the composition of ORS, the rate of intake also affects metabolic acidosis.

A few studies have already been conducted to explore the effectiveness of maintenance oral rehydration in patients with no clinical signs of dehydration. For this purpose, solutions containing Na^+ concentrations ranging from 30–90 mmol/liter proved effective over a treatment period of 24 h (42a, 72, 90, 127, 130).

Critical Evaluation of the Clinical Efficacy of Organic Substrate-ORS

IT IS DIFFICULT TO ASSESS THE SPEED OF REHYDRATION ORS is mainly used to treat or prevent dehydration. Nevertheless, the primary objective of most of the clinical trials conducted to test new ORS was to reduce the duration and volume of diarrhea. In our opinion, it would probably be useful in the future to consider the reasons for this apparent discrepancy between the primary objective of the clinical trials and the physiological factors considered when attempting to improve intestinal water and electrolyte reabsorption and thereby the hydration status of the patients.

If the primary objective of a clinical trial is to assess the efficacy of rehydration, the outcome variables should constitute a reliable quantitative index of the hydration status of the patient. Although dehydration is fairly easy to recognize in the initial clinical examination in patients with acute watery diarrhea, the exact degree of dehydration is almost impossible to determine with the usual criteria. MacKenzie et al critically analyzed this problem (75) and found that the degree of dehydration is frequently overestimated by an average of 2–3%, with wide variability.

In addition, weight gain is a reliable index of rehydration during the initial treatment phase; in most clinical trials, weight gain is indeed reported. However, it is not a discriminant criterion, probably for two reasons: (*a*) in all studies in which a gain in weight was reported, the amount was essentially the same with the new ORS under investigation and with the reference G-ORS; and (*b*) the criterion for comparing the effects of two ORS is more likely to be an index of the speed of rehydration than of rehydration itself. This criterion has not been appropriately addressed in clinical trials involving new ORS. One can therefore conclude that the results obtained with ORS in which the electrolyte concentration was modified or in which organic substrates were used instead of or in addition to glucose show that the patients were rehydrated but do not indicate whether a substrate has any advantage in terms of the speed of rehydration.

As stated above, the primary objective of most clinical trials was to assess the efficacy of a new ORS in reducing the duration and volume of diarrhea. The results for these parameters differ considerably, but it is likely that fewer clinical trials have been published for which no significant effect was observed than for which a significant effect was observed. In this regard, the meta-analysis by Gore et al (48) is of particular interest because it was based on the data for a large series of clinical trials in which the effects of rice- and glucose-based ORS were compared. The results indicate that diarrhea is reduced when its etiology is cholera, but not when it stems from other etiologies.

STOOL OUTPUT AND DURATION OF DIARRHEA ARE NOT THE APPROPRIATE VARIABLES TO ASSESS REHYDRATION Dehydration is due to an increase in stool output, but ORS does not rehydrate by reducing stool output. Rather, it rehydrates by increasing water and electrolyte intake and absorption. In view of the enterosystemic cycle of water and electrolytes (Figure 1), increasing the intake of ORS results in ORS absorption with only marginal effect on stool output, up to a threshold of absorption above which the ingested ORS is not entirely reabsorbed (97, 131). The absorbed ORS rehydrates, while the malabsorbed ORS remaining in the intestinal lumen increases the volume of watery diarrhea. The absorption threshold could perhaps be raised by the use of appropriate substrates. For example, it is well established in physiology that the addition of alanine to glucose further stimulates sodium absorption (116). Maltodextrin may also replace glucose in order to reduce ORS osmolality and stimulate the glucose absorptive process along the entire length of the small intestine by gradual digestion of the maltodextrin (23). However, the clinical results do not indicate that such addition or replacement clearly reduces stool volume. In addition, Benbouabdellah et al (personal communication) found no differences between the ^{13}C enrichment of CO_2 produced by children rehydrated with ORS containing naturally enriched ^{13}C maltodextrins and the

enrichment produced by ORS containing ^{13}C glucose, which suggests that the two substrates were equally absorbed and metabolized during rehydration.

It has been suggested that cereals might have a specific antidiarrheal effect in addition to their carbohydrate effect, on account of the functional peptides they contain. This suggestion may stem from the discovery that β-casein contains a peptide sequence called β-casomorphin that can bind to opiate receptors (52). In addition, a nonmetabolized analog of β-casomorphin was found to inhibit the secretion induced by cholera toxin in a rat model (13). However, no such peptide sequence has been identified yet in rice.

EARLY FEEDING IS BY ITSELF AN IMPORTANT SOURCE OF ORGANIC SUBSTRATES In order to accurately interpret the effect of the presence of an organic substrate in ORS on the duration of diarrhea, one must remember that patients are fed as soon as they are rehydrated, i.e. 4–8 h after rehydration is initiated, or immediately if they are not dehydrated. Therefore, it is difficult to imagine that mixing 20 g of an amino acid such as glycine or alanine into a standard food could have an effect on water absorption specifically different from that of 20 g of glucose. Furthermore, a beneficial effect on the duration of diarrhea can only be expected if large quantities of ORS are given with a low food intake, which might explain why ORS with an organic substrate or nutrient base have a positive effect in cholera patients with a high purging rate who cannot drink large quantities of ORS and eat at the same time.

The same results are obtained when rice powder ORS is given to children on a rice diet. However, in this particular case of cereal- or legume-based ORS, expectations were fulfilled because it was clearly demonstrated that solutions made with local products could replace the manufactured G-ORS and rehydrate children and possibly adults as well, although fewer of the latter have been tested.

ORS: A NUTRIENT OR A TREATMENT TO IMPROVE EARLY BEHAVIOR? One reason for developing organic substrate or nutrient-based ORS is to improve nutritional outcome. This issue has always led to confusion and misunderstanding, which we attempt to clarify here. On the one hand, clinicians working in reference hospitals, especially pediatricians, struggle with the treatment of malnourished dehydrated children: The rate of mortality in these patients is probably 10–30% (139). On the other hand, public health programs, and certainly the WHO program, have been based on the principle that by vigorously correcting dehydration, rehydration with G-ORS would allow patients to eat after a shorter time than would slow rehydration systems (22, 55, 71). In other words, the glucose in ORS is not considered a nutrient, but rather a drug that can improve eating behavior and therefore reduce the risk of malnutrition resulting from diarrhea. This hypothesis was tested by comparing the

growth of children in rural areas with and without access to ORS in cases of diarrhea. Indeed, those who received ORS had a better nutritional status than did controls (21). However, these studies were difficult to conduct as prospective randomized trials for obvious ethical reasons, and their results have therefore been challenged during the past three or four years (19, 21). Although neither the nutritional status nor the risk of mortality was directly related to the use of ORS, the methodology used to assess the causal relationship between the use of ORS and its long-term consequences for nutrition may not be optimal at present.

Critical Evaluation of the Clinical Efficacy of ORS According to Their Electrolyte Composition

Why ORS of different composition are equally effective is difficult to understand. In nearly all studies, the rehydration time was a preset period for which equal effectiveness was usually demonstrated. One possible way to discriminate between the effectiveness of different Na^+ concentrations in oral dehydration therapy would be to compare the exact rehydration times. Five studies in which the time was measured showed that with solutions containing 90 mmol/liter of Na^+, patients were rehydrated faster than with solutions containing lower Na^+ concentrations (28, 107, 111, 112). A precise definition of how to estimate clinical dehydration is rarely mentioned in any study but may be important, according to MacKenzie's recent work (75). The fact that the rehydration time, which was preset by different authors, varied from 4–24 h is also of interest. When rehydration was achieved within short periods of 4–8 h, the volume of ORS used varied from 12–30 ml/kg per hour (16, 58–60, 91, 107, 108, 121, 128–30). For patients rehydrated in 24 h, the volumes used were always smaller than 10 ml/kg per hour (1, 4, 7, 42a, 53, 58–60, 64, 70, 72, 81, 84, 85, 93, 98, 99, 101, 119, 125, 127, 130). Conversely, diarrheal volume almost never changed with the different speeds of rehydration and was usually in the range of 3–7 ml/kg per hour, except in the case of severe cholera diarrhea. Also worth noting are the very low failure rates obtained with all the different solutions and rehydration times used, for which diarrheal losses were remarkably constant and hydration volumes were closely related to rehydration times.

No studies have been conducted to accurately assess dehydration and rehydration or to explore the relationship between rehydration time and the mineral content of rehydration solutions. Such an approach would enable investigators to evaluate whether the shortest rehydration time would allow the fastest resumption of normal feeding together with effective maintenance of oral rehydration.

POSSIBILITIES FOR IMPROVING ORS

Assessement of the End Point of Rehydration

The method for comparing the efficacy of a new treatment of acute diarrhea with dehydration with the reference treatment, i.e. G-ORS and early feeding, is well defined, and the methods of measuring the gain in weight and the duration and volume of diarrhea are well established. Most clinical trials designed to test the efficacy of ORS containing organic substrates were conducted according to the rules for randomized clinical trials. However, as stated above, the efficacy of these solutions in accelerating rehydration was not assessed, primarily because there is no simple way to do so. Adequate methods should therefore be devised to improve the usefulness of future clinical trials.

A comparison of the criteria for the clinical evaluation of dehydration based on objective measurements with the speed of dehydration (12) would be desirable. In other words, how useful is the absence of tears or dryness of the tongue when assessing the degree of dehydration? Skin turgor is an obvious sign of dehydration, but is it a relevant criterion of the dynamic aspect of the hydration status? Just as the absolute bilirubin concentration is not sufficient to evaluate the risk of evolution of neonatal jaundice, specific dynamic indexes of dehydration and rehydration must be defined.

The end point of rehydration must also be assessed in clinical trials. In the early 1960s, pediatricians proposed several indicators, including the K^+:Na^+ ratio; changes in the pH or osmolality of the urine and blood; variations in glucose, urea, or protein concentrations; and variations in specific gravity or hematocrit (7, 27, 51, 77, 86). The measurements obtained for these indicators have been extensively studied from a pathophysiological point of view. Thus the K^+:Na^+ ratio in urine was examined as an index of hyperaldosteronism secondary to blood volume restriction, and urinary pH and osmolarity were investigated as indexes of temporary alterations in kidney distal tubule functions.

However, these indicators have not been evaluated in terms of their sensitivity and specificity in assessing dehydration. In principle, one could compare the measurements obtained for these indicators with those obtained using a reference method for measuring total body water or extracellular and intracellular water. In this regard, continuous monitoring of body weight on an electronic balance, monitoring of bioelectric impedance, and dilution techniques of heavy water and nuclear magnetic resonance have been proposed, but in a different context (10, 40, 41, 43, 79, 96, 142).

Evaluating the Effects of ORS in Severely Malnourished Children

A possible second line of investigation is the evaluation of ORS in malnourished dehydrated children. Interestingly, most of the published clinical trials

were conducted with well-nourished or moderately malnourished children. However, malnutrition is associated with metabolic disorders that merit serious consideration in the management of rehydration (77). These disorders include altered body water distribution in kwashiorkor and in marasmus and reduced potassium content and energy reserves, with minimal fat and muscular mass and a decrease in exocrine pancreatic secretion, including amylase secretion (139). A recent clinical trial conducted in marasmic children with acute diarrhea and dehydration found rice-ORS to be as effective as G-ORS (114). In this study, the rate of ORS intake was reduced by one third compared with standard rehydration recommendations in order to avoid overhydration. At present, the literature does not contain sufficient data to allow for firm or permanent recommendations for the use of ORS among malnourished children in specific settings (20, 47).

Organic Substrates with Intestinal Metabolic Activity

The third line of investigation concerns the choice of substrate for use in ORS. The available results clearly show that local cereals or legumes are effective alternatives to glucose. Moreover, well-defined substrates, chosen for their effect on Na^+ absorption in the small intestine, do not have any significant therapeutic advantage over glucose. Another field of study involves a search for substrates with specific metabolic effects. This approach has yielded results that indicate that L-glutamine may be of particular interest for several reasons. First, L-glutamine stimulates intestinal absorption in piglet jejunum and rabbit ileum by a mechanism distinct from, and additional to, that of glucose (34), although this effect is less marked in experimental rotavirus (116, 117) and enteropathogenic *E. coli* infections (94). Additionally, both in cholera patients (Van Loon, personal communication) and during PGE_1-induced hypersecretion, L-glutamine was well absorbed in the human jejunum at a rate similar to that of glucose and stimulated water and electrolyte absorption. Second, L-glutamine supports the metabolism of intestinal epithelial cells, both as a major fuel (9) and as a precursor for purine and pyrimidine structures present in nucleotides. Oral intake of glutamine stimulates mucosal growth and repair (45). Lastly, in humans, glutamine is a major nitrogen carrier in vivo and plays a key role in protein metabolism in relation to muscular mass. Moreover, recent results indicate that L-glutamine may inhibit lipolysis (35) and stimulate the immune system.

In summary, L-glutamine could be considered a possible substrate for ORS because of (*a*) its direct effect on Na^+ reabsorption and (*b*) its selective intestinal metabolic effect. The latter effect could be used to spare other sources of energy from the body, e.g. muscular and fat mass, and from food, e.g. glucose and fatty acids.

Substrates Specifically Targeted for the Colon

Finally, it may be of interest to identify the substrates that could be used specifically by the colon. Thus far, organic ORS substrates have been chosen for their effect on the small intestine. In fact, however, the colon plays an important role in the reabsorption of water and electrolytes. This role was examined in healthy adult volunteers whose stomach was perfused with isotonic saline solution at an increasing rate. Diarrhea occurred when the fluid entered the colon at a flow rate of $\geq$ 6.3 ml/min (97). In a different experiment, a threshold for carbohydrate was also observed (131). This threshold rose in transmissible gastroenteritis of three-day-old and three-week-old piglets (8). The infected animals failed to absorb fluid or glucose in the small intestine. However, unlike the small intestine of these three-day-old animals, the large intestine of older infected piglets exhibited increased fluid absorption ~ six times that of the control. This compensatory response prevented the onset of diarrhea in the older animals. The significance of a colonic threshold for water and glucose loading lies in the three main activities of the colon: motility, absorption, and intraluminal bacterial metabolism.

Secondary hyperaldosteronism, a physiological response that stimulates colonic Na^+ absorption (7), occurs during dehydration. Moreover, anaerobic colonic flora produces short-chain fatty acids that also stimulate colonic Na^+ absorption but via a different cellular mechanism (18a, 18b, 113).

In addition to the physiologic response of the colon, the effect of the carbohydrates metabolized in the colon on stool output in diarrhea should also be examined. The carbohydrate chosen could have many forms, but to enable local food to be tested in this research, it might consist of uncooked powdered rice, maize, sorghum, or millet. Some of these uncooked cereals are successful in the management of children with glycogenosis (29, 134). A portion of the carbohydrates may be absorbed in the small intestine, and the remainder may be metabolized by the colonic bacteria under anaerobic conditions into short-chain fatty acids. The nature of some fatty acids enables them to increase NaCl absorption, reduce colonic motility, and provide a source of energy (44, 120).

The production of short-chain fatty acids by colonic bacteria can be induced in a few days, but this length of time precludes the use of this treatment in acute diarrhea. The production of short-chain fatty acids is pH dependent, i.e. it decreases below pH6. In theory, therefore, the addition to ORS of microorganisms that maintain the intraluminal pH above 6 could also maintain short-chain fatty acid production by exerting a probiotic effect (46, 78, 140).

In summary, two groups of organic substrates have been proposed as glucose substitutes or as glucose supplements in ORS: local cereals and legumes, and chemically defined substrates. These substrates were primarily selected for three reasons: (*a*) to stimulate Na^+ absorption by cotransport with Na^+ similar

to but different from glucose-Na^+ cotransport, (*b*) to reduce the osmolality of the solution, and (*c*) for their local availability to patients with acute diarrhea who do not have access to G-ORS. These substrate-ORS have been tested in well-conducted clinical trials and compared with the standard G-ORS.

The therapeutic efficacy of ORS containing these organic substrates did not exceed that of glucose ORS, with the exception of rice in patients with cholera. These results indicate that local products can be used for rehydration. In addition, these data could serve as the starting point of four areas of research: (*a*) measurement of the speed of rehydration, which would enable comparison of the efficacy of different solutions; (*b*) development of ORS for the rehydration of children with severe malnutrition; (*c*) evaluation of the efficacy of substrates such as L-glutamine that act both on Na^+ absorption and on the energy metabolism of the cells lining the intestinal epithelium; and (*d*) evaluation of the effect of the substrate on the colonic function of salvaging water, electrolytes, and possibly nutrients.

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