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Improving the Efficiency and Effectiveness of Oral Rehydration Solutions: From Physiology to Clinical Practice

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Abstract

Dehydration secondary to diarrhoea continues to claim the lives of over a million children each year. Although effective in reversing dehydration and preventing death, oral rehydration solution (ORS) utilization in many communities remains low partly because it does not reduce diarrhoea severity or duration. Advances in understanding of colonic ion and water absorption provide an opportunity to harness the considerable capacity of the colon to absorb fluid. Short chain fatty acids (SCFA), produced by bacterial fermentation of unabsorbed carbohydrate in the colon, enhance colonic sodium water absorption and prevent chloride secretion in diarrhoea. SCFA concentration in the colon can be increased by ingesting amylase resistant starch that escapes small bowel digestion. Clinical trials using amylase resistant starch as adjunct to ORS show that diarrhoea duration and severity are reduced in adults with cholera and in children with non-cholera diarrhoea. This provides a new strategy to enhance ORS utilization in developing world communities.

Key Words: oral rehydration, ORS, short chain fatty acids, sodium water absorption.

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Introduction

Diarrhoea continues to be a major cause of childhood morbidity and mortality in developing countries, accounting for 1.5 to 2 million deaths annually (1). The principal cause of diarrhoeal mortality is dehydration, or the loss of fluid and salt from the body. The degree of dehydration determines the occurrence of symptoms and complications. Low levels (2% loss of body weight or more) impair cardiovascular and thermoregulatory responses (2). When fluid loss exceeds 10% of body weight the disturbance of homeostasis becomes life threatening. In severe dehydration, rehydration needs to be achieved intravenously (3). In less severe dehydration (and in the absence of significant vomiting) the gastrointestinal tract has the capacity to absorb fluid rapidly, and can be the route of rehydration. An understanding of the physiology of intestinal transport processes led to the development of oral rehydration solution (ORS), an excellent example of translational research (4). ORS was hailed as one of the great medical achievements of the twentieth century because of its simplicity and its scope to save lives (5). However, despite its ability to reverse dehydration when properly used, ORS utilisation remains poor in many communities. One of the reasons for low ORS usage rates is that ORS does not reduce severity (i.e., frequency or quantity of stooling) or duration of diarrhoea (6). This led to multiple attempts over the years to improve ORS and produce a super-ORS. The first ORS was formulated to treat patients with cholera and an iso-osmolar (osmolarity equivalent to that of plasma) solution was used. However, the realisation that this could cause hypernatraemia in infants and that absorption of fluid from a hypo-osmolar solution was better than from an iso-osmolar solution (7,8) led to the recommendation in 2002 of a hypo-osmolar ORS for universal use in diarrhoea (9).

Physiological basis for absorption and secretion of electrolytes and water from the intestine

Water absorption from the intestine and colon is passive and depends on the active absorption of ions (eg. sodium) or nutrients (eg. glucose and aminoacids) (10). Active absorption takes place against concentration or electrochemical gradients and is dependent on expenditure of energy. Sodium absorption is the major driving force for water absorption. Chloride, the other ion in common salt, is either actively absorbed by epithelial cells

coupled to sodium or absorbed passively through the paracellular pathway. The transport proteins responsible for sodium absorption or for sodium chloride absorption are now well characterised, and their distribution varies along the intestine and colon, leading to differential absorptive properties of the different segments of the gastrointestinal tract (Table 1). The upper small intestine is responsible for absorption of glucose and other nutrients and water absorption usually follows these. The intercellular

Table 1 : Pathways for active ion absorption in different segments of the intestine and their relationship to ORS design.

Segment of intestine	Absorptive pathway	Effect of aldosterone	Effect of cAMP & other secretagogues	Utilisation in ORS
Jejunum	Na-H exchange	Inhibited	Inhibited	—
	Glucose-Na cotransport	—	—	Standard, Hypo-osmolar
	Aminoacid-Na cotransport	—	—	Aminoacid-ORS
Ileum	Coupled Na-Cl absorption	Inhibited	Inhibited	—
	Na channels	Enhanced	—	—
	Glucose-Na cotransport	—	—	Standard, Hypo-osmolar
	Aminoacid-Na cotransport	—	—	Aminoacid-ORS
Proximal colon	Coupled NaCl absorption	Inhibited	Inhibited	—
	SCFA-linked NaCl transport	—	—	Starch-ORS, CHO-ORS
Distal colon	Na channels	Enhanced	—	—
	SCFA-linked NaCl transport	—	—	Starch-ORS, CHO-ORS

Na-H exchange (NHE) occurs via various NHE isoforms; this process is electrically neutral. Na channels allow only sodium transport, in the process generating an electrical current, i.e. electrogenic. Coupled Na-Cl absorption results from coupled Na-H and Cl-HCO_3 exchanges, and is electroneutral. Glucose- and aminoacid-linked Na cotransport generate electrical currents. SCFA-linked NaCl absorption is electroneutral and operates through conjunction of Na-H, Cl-SCFA and SCFA-HCO_3 transporters.

junctions between epithelial cells in the jejunum are very permeable or 'leaky' and allow the rapid movement of fluid either into or out of the intestinal lumen depending on the balance between osmotic forces in the lumen of the intestine and the blood. Thus, if a meal or beverage with high sugar content (i.e. high osmotic load) is ingested, fluid quickly rushes into the lumen of the jejunum. On the other hand, rapid absorption of water takes place if the fluid is of lower osmolarity than plasma. In the ileum, different processes for sodium absorption predominate, and the junctions between the epithelial cells lining the intestine are less 'leaky', causing greater dependence of water absorption on sodium absorption. Sodium absorption from the ileum can take place even from a solution with a sodium concentration of 35 mmol/l (11). The epithelium of the colon also has a great capacity to absorb sodium, and the intercellular junctions between epithelial cells are 'tight'. These two attributes confer upon the colon the ability to dehydrate the luminal contents. Perfusion studies have demonstrated sodium absorption from the colon even when the concentration of sodium in the luminal solution is as low as 25 mmol/l (12). The adult human colon absorbs about 1500 ml water, 190 mmol sodium, and 95 mmol chloride in a day, but can absorb 5 or 6 litres of fluid

Table 2 : Approximated net absorption from lumen or secretion into lumen in ml per day from the digestive tract in health and in diarrhoea. Cholera is used as an extreme example of the diarrhoeal state, and three situations with no ORS, glucose-ORS or starch-ORS are depicted.

	Healthy adult	Cholera		
		No ORS	Glucose ORS	Starch ORS
Digestive secretions	7000	12000	12000	12000
Oral intake	2000	2000	12000	12000
Small bowel absorption	7500	2000	12000	12000
Inflow into colon	1500	10000	12000	12000
Colonic absorption	1300	500	500	6000
Stool output	200	9500	11500	6000

in a day when stressed (13,14). The hyperaldosteronaemia that accompanies dehydration can increase the ability of the colon to conserve sodium and fluid through activation of sodium channels (15). These issues are important in the design of ORS.

The major active force driving fluid secretion in the intestine is the secretion of chloride ions from the crypts of the intestines (16), a process which is turned on by cyclic nucleotides such as cyclic AMP and cyclic GMP and by calcium (17). Chloride secretion results in the passive movement of sodium (to maintain electrical equilibrium) and water (to maintain osmotic equilibrium) from the blood into the intestinal lumen across paracellular pathways. Secretion of other ions such as potassium and bicarbonate also occurs actively, but does not usually lead to significant fluid secretion.

Alterations in ion and water transport in diarrhoeal disease

The mechanisms responsible for sodium and water absorption in the healthy intestine are significantly altered in diarrhoeal disease. There is inhibition of some normal absorptive processes and augmentation of some secretory processes, resulting in net loss of fluid into the lumen of the intestine. Chloride secretion occurs through chloride channels in the apical membrane of the epithelial cell that are activated by a number of second messengers including cyclic AMP, cyclic GMP and calcium-calmodulin (17). Water is thought to move passively secondary to osmotic forces, and this may involve aquaporin channels (18). Sodium-hydrogen exchange and coupled NaCl absorption, the transport mechanisms responsible for the bulk of intestinal sodium absorption in health, are inhibited in diarrhoea due to the cellular effects of the second messengers that mediate diarrhoea. Glucose-linked or amino acid-linked sodium absorption in the intestine is not inhibited in diarrhoea, and this is the rationale for the use of ORS (4). By giving sodium and other salts along with glucose, it is possible to stimulate sodium and water absorption from the intestine even though fluid secretion (which is secondary to active chloride secretion) into the lumen of the intestine continues alongside.

Physiological pathways to optimise ORS efficiency and their effect on ORS development

ORS was introduced in the 1960s following the recognition of glucose-linked sodium absorption as an important pathway of sodium and fluid absorption in the intestine. The basis of the use of ORS is that the

enterotoxins causing diarrhoea do not impair sodium absorption linked to specific substrates (glucose and amino acids). Although it enhances fluid absorption from the secreting intestine, the glucose-based ORS did not reduce intestinal secretion or diarrhoea, and sometimes paradoxically increased diarrhoea (19). Efforts were therefore made to improve the efficiency of ORS to produce a "super" ORS that, in addition to reversing dehydration, would reduce the severity and duration of diarrhoea. The use of amino acid substrates (glycine, alanine, and glutamine) in ORS to supplement the effect of glucose on sodium absorption did not prove advantageous compared to glucose ORS (20). Glutamine, of particular interest because of its role in providing energy to intestinal epithelial cells and its effects on immunity, was effective in reducing small intestinal secretion in experimental models of diarrhoea, but was not better than glucose-ORS in clinical trials (21). Maltodextrins and cereal-based ORS were introduced in an attempt to change the carbohydrate substrate in ORS, by providing glucose in the lumen at a reduced osmotic penalty compared to glucose ORS. While maltodextrin-ORS was not any better than glucose ORS, rice-based ORS has been shown in multiple clinical trials to significantly shorten diarrhoea particularly in patients with cholera (22). Early re-feeding of patients, commencing within four hours after initiation of rehydration, has become the standard of care in diarrhoea, and may achieve some of the effects of rice ORS. The ability of rice ORS to shorten diarrhoea in cholera has been attributed to the low osmolarity of the solution, as well as a 'kinetic advantage' resulting from the hydrolysis of starch end-products in close proximity to the sodium glucose cotransporter (23). However, other factors including a possible anti-secretory factor found in rice could contribute to its effect in cholera (24).

A major advance in the ongoing refinement of ORS came about with the introduction of reduced osmolarity (hypo-osmolar) ORS (9,25). The glucose ORS originally recommended by the World Health Organization had an osmolarity of 311-331 mOsm/kg, broadly similar to that of plasma. Physiological studies established that reducing the osmolarity of luminal solutions would increase absorption of sodium and water from the proximal small intestine in both normal and secreting intestine (7,8). Multiple clinical trials of reduced osmolarity ORS showed that stool output and diarrhoea duration were reduced by approximately 20% compared to the

older glucose-ORS and this solution is now recommended for use in all situations by the World Health Organisation (26).

All the interventions described up to now were targeted at small intestinal fluid absorption. While it is true that the small bowel has the capacity to absorb more than 12 litres of fluid per day in health, this capacity is compromised in diarrhoeal disease. The colon absorbs about 1.5 liters of water per day in health; when stressed, as in diarrhoea, it can absorb up to 6 liters of water per day (13,14). This reserve capacity of the colon to absorb fluid, which can help to minimize faecal fluid losses, is compromised in diarrhoea (27). Therefore it is likely that interventions that enhance colonic absorption may reduce severity and shorten illness in infective diarrhoea. Short chain fatty acids (SCFA), represented by acetate, propionate and butyrate, are found abundantly in the human colon constituting the major anions in stool at concentrations of 100-130 mmol/L. They significantly increase sodium and water absorption from the normal human colon, through a process of linked ion exchanges across the luminal membrane of colonic epithelial cells (28). Studies in experimental animals *in vivo* and *in vitro* suggest that SCFA-linked sodium absorption is not inhibited, and may even be up-regulated, by cyclic nucleotides (29,30). These studies also suggest that SCFA (in particular butyrate) inhibits active chloride and fluid secretion in the colon (28). Faecal SCFA are reduced in cholera or other forms of diarrhoea (31). Delivery of SCFA to the colon is an issue since orally ingested SCFA will be rapidly absorbed from the upper gastrointestinal tract. Unabsorbed carbohydrates such as amylase resistant starch, non-starch polysaccharides (eg. pectin), and fructo-oligosaccharides, can potentially be fermented in the colon to SCFA (32). Starch has a particularly favourable profile of fermentation with significant production of butyrate (33). Incubation of stool from cholera patients with starch resulted in the production of SCFA, indicating that the colonic flora in cholera retained the capacity to ferment carbohydrate (34). On the basis of these studies, amylase resistant starch was given to patients with cholera along with ORS, assuming that SCFA resulting from its fermentation would increase colonic fluid absorption. This resulted in significant reduction in diarrhoea (approximately 30% reduction in stool volume after 12 hours) and in diarrhoea duration (reduced by approximately 37%) in the test group compared to glucose ORS (35). Resistant starch ORS was also significantly better than rice ORS.

These studies were also undertaken in children with predominantly non-cholera diarrhoea and amylase resistant starch was shown to shorten diarrhoea in this situation as well (36). Since reduced osmolarity ORS is now the default ORS and since its effects on absorption are primarily in the small bowel, we reasoned that adding amylase resistant starch to reduced osmolar ORS would have an incremental effect in shortening diarrhoea. This was tested in an animal model of diarrhoea and found to be indeed so (37), and was also found to shorten diarrhoea in adults with severe dehydrating diarrhoeal illness (38).

Interestingly, other carbohydrate substrates have also been tested for effects on diarrhoea. In a study in children with diarrhoea, partially hydrolyzed guar gum led to 18% reduction in diarrhoea duration and a trend to reduced stool volumes compared to glucose ORS (39). Another study in children using a mixture of unabsorbed carbohydrates failed to show an effect (40), but this was likely because of the low concentration of the carbohydrate substrate that was given. Unabsorbed carbohydrates, green banana (containing amylase resistant starch) and pectin, also hastened resolution of diarrhoea and clinical recovery in children with persistent diarrhoea (41).

Finally other adjunct therapies, notably zinc, improve the effectiveness of ORS, helping in early recovery from illness and prevention of complications such as persistent diarrhoea and malnutrition. The use of zinc as adjunct therapy to ORS is now recommended in children with acute diarrhoea.

In conclusion, multiple factors continue to hinder the general acceptance of rehydration fluids and beverages in the community. Our current understanding of intestinal absorptive and secretory physiology can be exploited to improve ORS characteristics and efficiency which can be confirmed in clinical trials. Operational research to optimize delivery of the efficient ORS will likely further enhance the effectiveness of ORS and further reduce diarrhoeal deaths in children in accord with the Millenium Development Goals.

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