Journal of Pediatric Gastroenterology and Nutrition
39:325–327 © October 2004 Lippincott Williams & Wilkins, Philadelphia

Editorial

Resistant Starch—An Adjunct to Oral Rehydration Solution: Not Yet Ready for Prime Time

*Henry J. Binder and †B. S. Ramakrishna

**Section of Digestive Diseases, Yale University, New Haven, CT; †Gastrointestinal Sciences, Christian Medical College, Vellore, Tamil Nadu, India.*

Oral rehydration therapy for the treatment of acute diarrhea has been acclaimed as one of the most important therapeutic advances of the past century (1). The development of oral rehydration solution (ORS) some 4 decades ago was an immediate consequence of physiologic studies of glucose-stimulated Na absorption in the small intestine in humans and experimental animals. The physiologic basis for ORS was the demonstration that absorption and secretion are separate and distinct processes in the intestine; cyclic nucleotides induce fluid secretion without affecting glucose-stimulated Na absorption; and glucose enhances Na and fluid absorption without modifying fluid secretion.

Oral rehydration therapy, using a relatively isoosmolar glucose-electrolyte solution with the addition of a base (either bicarbonate or citrate), rapidly became adapted throughout the developing world and was found to reduce substantially the morbidity and mortality of acute diarrhea in children, especially in those younger than 5 years. The efficacy of the standard World Health Organization (WHO)-ORS was based on the correction of the dehydration and metabolic acidosis that occurs during an episode of severe diarrhea, e.g., cholera. Unfortunately, WHO-ORS did not dramatically reduce stool output (i.e., diarrhea), so during the next 20 years there were multiple efforts to develop a "super" or "super-super" (i.e., an improved ORS that would reduce diarrhea, in addition to its correction of dehydration and metabolic acidosis).

Most of these efforts focused on the inclusion of different dietary substrates and were directed to stimulation of Na absorption in the small intestine. Thus, several studies evaluated amino acids without evidence of dramatic improvement compared with the gold standard of WHO-ORS. Additional studies with food-based sources of glucose (e.g., rice-based, cereal-based ORS) demonstrated improved efficacy in the treatment of acute diarrhea (2). In general, these newly developed ORSs were found to be most effective in adults with cholera but substantially less so in children with diarrheal episodes secondary to noncholera etiologies. These different food-based ORSs all contained polymers that, following their digestion by pancreatic and intestinal enzymes, resulted in glucose production. As a consequence, these solutions frequently were used with a reduced osmolality. Subsequent studies proposed that the primary efficacy of these food-based solutions was their hypo-osmolar composition (3). All of these solutions are generally believed to result in enhanced small intestinal fluid absorption.

Nonetheless, efforts continued to develop other improved ORSs. These more recent approaches have sought to use short-chain fatty acid (SCFA)-stimulated Na absorption in the large intestine as an adjunct to glucose-stimulated Na absorption in the small intestine (4). SCFAs are not normal constituents of the diet but are produced primarily in the colon by colonic bacteria from nonabsorbed carbohydrate (5). This approach with SCFAs was based on the unexpected observation that cholera toxin and cyclic nucleotides did not inhibit SCFA-stimulated Na absorption from the colon either in vivo or in vitro (6,7). These experimental observations were surprising because the mechanism of SCFA-stimulated Na-Cl absorption includes a luminal membrane Na-H exchange (NHE) that was coupled to SCFA uptake via luminal membrane SCFA-HCO_3 and Cl-SCFA exchanges (8). Previous studies had established that intestinal Na-Cl absorption represented the coupling of Na-H and Cl-HCO_3 exchanges in the luminal membrane and that cyclic nucleotides inhibit small intestinal Na-Cl absorption as a result of their inhibition of Na-H exchange. Thus, it appeared that cyclic nucleotides reduced HCO_3-dependent Na-Cl absorption by virtue of their inhibition of Na-H exchange but did not affect Na-H exchange when the latter is linked to SCFA-stimulation of Na-Cl absorption.

Supported in part by Wellcome Trust.

This apparent paradox was resolved in studies of the effect of cyclic AMP on the two different Na-H exchange isoforms (NHE-2 and NHE-3) in the luminal membrane of both the small and large intestine (9). These experiments demonstrated that HCO_3-dependent Na absorption was linked to NHE-3 isoform but not to NHE-2 isoform. In contrast, SCFA-dependent Na absorption was coupled to both NHE-3 and NHE-2 isoforms. The final piece of the initial paradox was the demonstration that cyclic AMP inhibited NHE-3 isoform but also increased the activity of NHE-2 isoform. Thus, cAMP inhibits HCO_3-dependent Na-Cl absorption because it down-regulates NHE-3 isoform, which is the only NHE isoform that mediates HCO_3-dependent Na-Cl absorption. In contrast, butyrate-dependent Na-Cl absorption is not altered by cAMP because cAMP upregulates NHE-2 isoform which, like NHE-3 isoform, can mediate butyrate-dependent Na-Cl absorption.

These observations provided the basis for the proposal that ORS plus a poorly digested starch (i.e., one that was relatively resistant to amylase digestion), would result in increased delivery of carbohydrate to the colon; that in turn would result in increased production of SCFA; the latter would enhance Na and fluid absorption from the colon, despite increased amounts of cyclic nucleotides in colonic epithelial cells. Thus, this speculation raised the possibility that the use of amylase-resistant starch (RS) would capitalize on the absorptive capacity of the large intestine for fluid and electrolytes to augment absorption from the small intestine after ingestion of WHO-ORS.

To test this novel hypothesis that RS when added to ORS would result in enhanced colonic fluid absorption and, as a consequence, in reduced stool output, it was first necessary to demonstrate that RS was fermented to SCFAs by the bacteria in diarrheal stool (i.e., in different diarrheal illnesses there had not been a change in the fecal flora to one with a decreased fermentation capacity). Studies at Christian Medical College in Vellore, India, confirmed that SCFAs were produced when stool from patients with cholera was incubated in vitro with RS (10). This observation provided the basis for proceeding with a double-blind, randomized clinical trial of adult patients with cholera who were treated with RS-ORS, rice flour-ORS, or WHO-ORS (4). The RS used in this study was high-amylose maize starch produced from Australian maize. Ramakrishna et al. (4) demonstrated that patients who received RS-ORS had both a significantly reduced stool output and a shorter time to the first formed stool when compared with the other two treatment groups in this study. Of potential importance was that the first decrease in stool output was observed in the second 12-hour stool collection, with greater decreases seen in the subsequent two 12-hour stool collections. These observations provided evidence that RS-ORS might be the next super ORS, but additional observations would be required before the search for a new ORS was considered successful. These experimental results raised the additional possibility that at least part of the effectiveness of meal-based or cereal-based ORS might be related to the fermentation of nondigested food carbohydrates to SCFAs in the colon, and not solely a result of their hypo-osmolality. Additional studies are required before this alternate suggestion will be widely accepted.

To assess whether ORS containing nondigestible carbohydrate (RS equivalent) is better than standard ORS in children, Hoekstra et al. (11) recently completed a multicenter controlled trial in children with acute noncholera diarrhea. The results of this study, reported in this issue of the *Journal*, did not demonstrate a superiority for RS-equivalent ORS but observed that there was no difference between the intervention and the control group with regard to the two primary end points: stool output and time to the first formed stool.

Does this end the trail of another potential candidate (i.e., RS-ORS) for the super ORS? We suspect not because there were major differences in the study designs of these two randomized controlled studies of RS-ORS: (1) different RS formulations; (2) different RS concentrations; (3) varying degrees of severity of diarrhea; (4) different ages of the subjects; and (5) different etiologies of their diarrhea.

Different formulations of RS were used in these two studies (4,11). In contrast to the high amylase maize starch (HAMS) used in the Indian study, the pediatric study conducted by members of the ESPGHAN used as their RS equivalent a mixture of nondigestible carbohydrates (NDC) whose four major constituents were soy polysaccharide, inulin, gum arabic, and fructo-oligosaccharides. The hypothesis upon which RS-ORS is based is that the colonic bacteria metabolize RS to SCFAs, which enhance colonic fluid and Na-Cl absorption. The choice of RS is not inconsequential because different formulations of RS may not be fermented to SCFAs (especially butyrate) as effectively as others. Starch is fermented rapidly and preferentially to butyrate, compared with other nondigestible carbohydrates, and butyrate stimulates colonic Na absorption to a greater extent than do other SCFAs (e.g., propionate, acetate) (12).

The concentration of the nondigestible carbohydrate used may be critical to the resulting concentration of SCFAs established in the colonic lumen by fermentation. The current multicenter study used NDC concentrations of 1 g/100 mL of ORS, which is substantially lower than the RS concentration of 5 g/100 mL used in the study by Ramakrishna et al. Rabbani et al. (13) used a concentration of green banana of 25 g/100 mL or pectin at 1.5 g/100 mL, which both were efficacious in reducing diarrhea in children with persistent diarrhea. Alam et al. (14) used partially hydrolyzed guar gum as an NDC in a dose of 2 g/100 mL. The current study was the only one to use a mixture of carbohydrates, unlike the others, in

which the source of NDC usually was a single defined component (i.e., starch, pectin, or guar gum).

Also critical is whether the bacterial flora of the children in the current study was capable of metabolizing the NDC used in this study (or any RS) to SCFA. Ramakrishna et al. (10) established before the initiation of their study that SCFAs were produced when the stool from patients with cholera was incubated with HAMS. Both the type of RS and the enteric flora of these subjects are critical for SCFA production. The possibility exists that (1) the enteric flora of boys younger than 3 years (the study group in this trial) normally do not ferment all or certain carbohydrates as well as that of adults; (2) the enteric flora in these children was changed by their noncholera diarrhea such that the ability to produce SCFAs was reduced; or (3) the particular source of RS used in this study (NDC) was not metabolized to SCFA as effectively as HAMS. The studies of Rabbani et al. (13) and Alam et al. (14), both using NDCs in children, demonstrated evidence of a shortened duration of diarrhea in their treatment group. The issue of whether SCFAs were produced is not theoretical because Argenzio et al. (15) found in a study of a transmissible gastroenteritis virus in 3-day-old and 3-week-old pigs that newly born pigs developed severe diarrhea whereas the older pigs had minimal diarrhea as viral-induced jejunal fluid secretion was compensated by colonic production of SCFAs. The newly born pigs, in contrast to the 3-week-old pigs, did not produce SCFAs because their colonic flora did not contain the bacteria responsible for fermentation. Indeed, in a recently concluded study in noncholera diarrhea in children that was conducted at Christian Medical College, we have noted that diarrhea is modestly but significantly reduced in children treated with RS (i.e., HAMS-ORS) compared with ORS alone, in addition to standard rehydration therapy (unpublished observations).

Another important issue in the pediatric study was that the diarrhea was relatively mild, so it might be impossible to demonstrate improvement for any therapy compared with the control group. This issue is similar to the difficulty in establishing improved outcomes after acute myocardial infarction without stratifying according to complications (16). There also is concern with regard to the different composition of the ORS that was used in the two studies. The study of adults with cholera used WHO-ORS, which is approximately iso-osmolar (318 mOsm/kg H_2O), whereas the pediatric trial used a hypo-osmolar ORS with an osmolarity of 250 mOsm/kg H_2O and a reduced [Na] of 60 mEq. Hypo-osmolar ORS recently has been considered better than standard ORS. Thus, because a control group treated with a hypo-osmolar solution probably will have a better outcome than one treated with WHO-ORS, a new therapy might not demonstrate significant improvement when compared with a hypo-osmolar control group.

In conclusion, the issue of the incorporation of amylase-resistant starch in ORS has not been definitively established one way or another, and additional studies are required to establish the appropriate role of RS-ORS in the therapy of acute diarrhea. Such studies must include observations in children without cholera and in multiple age groups from a variety of locations throughout the developing world. When these studies establish the efficacy of RS-ORS, then RS-ORS will be ready for prime time!

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