ARTICLE

Assessing the Palatability of Oral Rehydration Solutions in School-aged Children

A Randomized Crossover Trial

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Objective: To compare the palatability of 3 oral rehydration solutions.

Design: Prospective, blinded, randomized, 3-period, 3-treatment crossover trial.

Setting: Emergency department of a tertiary care pediatric hospital.

Participants: Sixty-six children aged 5 to 10 years with concerns unrelated to the gastrointestinal tract.

Intervention: Each participant consumed as much of each solution as they desired during a 15-minute period.

Main Outcome Measures: The primary outcome was each child's rating of taste as measured on a 100-mm visual analog scale (worst taste, 0 mm; best taste, 100 mm). Secondary outcome measures were volume consumed, willingness to consume each liquid again, and the most favored liquid.

Results: All enrolled patients completed all 3 study periods. A significant carryover effect was detected for taste scores ($P=.03$), which were significantly different with and without adjustment for the carryover effect ($P<.001$). Unadjusted values were 65 mm for Pedialyte, 58 mm for Pediatric Electrolyte, and 23 mm for Enfalyte. Differences in mean volume consumed were not significant (Enfalyte, 15 mL; Pediatric Electrolyte, 17 mL; and Pedialyte, 22 mL [$P=.44$]). The proportion of children who would drink each solution in the future varied significantly between Enfalyte and Pediatric Electrolyte (odds ratio, 0.22; 95% confidence interval, 0.11-0.46) and between Enfalyte and Pedialyte (0.38; 0.25-0.57). There were differences in the identification of the best-tasting solution, with Pedialyte selected by 35 of 66 children (53%), Pediatric Electrolyte by 26 of 66 children (39%), and Enfalyte by 5 of 66 children (8%) ($P<.001$).

Conclusion: Sucralose-sweetened oral rehydration solutions (Pedialyte and Pediatric Electrolyte) were significantly more palatable than was a comparable rice-based solution (Enfalyte).

Trial Registration: clinicaltrials.gov Identifier: NCT00689312

Arch Pediatr Adolesc Med. 2010;164(8):696-702

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Previous analyses[1,2] indicated that acute gastroenteritis accounted for more than 20 million episodes of diarrhea and 1.5 million outpatient visits annually in the United States by children younger than 5 years. Therapy with oral rehydration solutions (ORSs) has reduced the mortality rates in underdeveloped countries,[3] but its effect has been less dramatic in developed regions.[4,5] Although this may be due to misperceptions regarding the need for extra time and effort to perform oral rehydration therapy,[6] one possible explanation is that ORSs may not be appealing to children owing to their poor palatability.[7] Consequently, many mild to moderately dehydrated children may refuse to consume ORSs.[8] In a survey of 235 North American pediatric emergency department physicians, 45% believed that the bad taste of ORSs caused more than 1 in 4 toddlers to refuse them (S.B.F., K.B., and V. Sivabalasundaram, BHSc, V. Bohn, BSc, E. Powell, MD, MPH, and D. Johnson, MD; unpublished data; May 1, 2010), and in a telephone questionnaire in the United Kingdom, it was cited as the main reason for not using an ORS as the first-line fluid.[7]

See also pages 703 and 784

Sodium is an essential element in the intestinal absorption of water, which occurs optimally when the glucose to sodium ratio is 1 to 1.[9] Consequently, ORSs all have a salty taste. Although the current marketplace contains numerous ORSs with variable sodium and glucose contents, they all contain a greater concen-

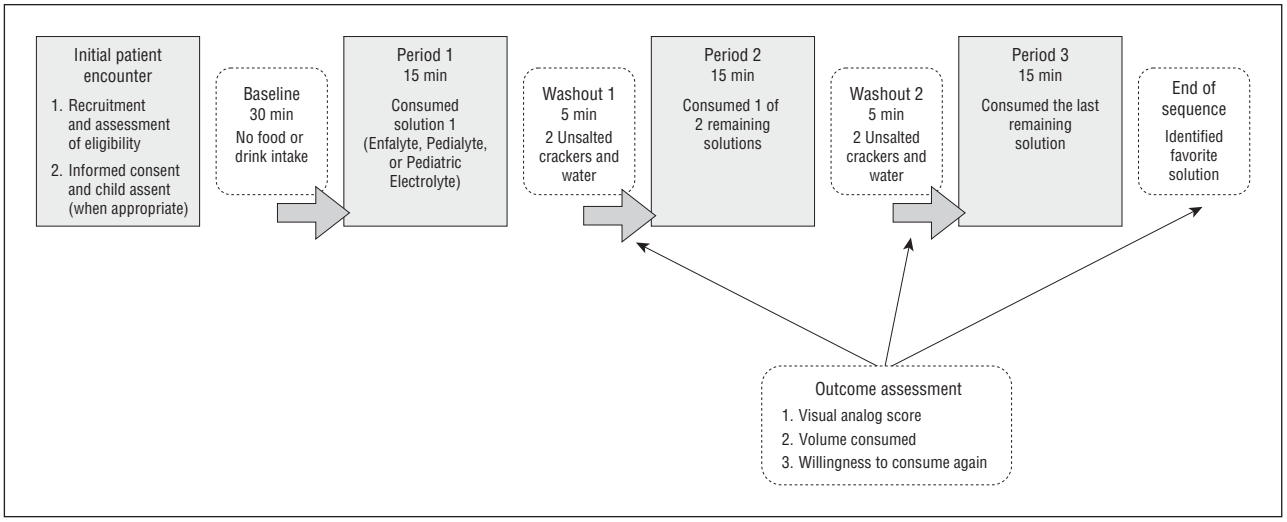

Figure 1. Study flow outline. Enfalyte manufactured by Mead Johnson Nutritionals, Evansville, Indiana; Pedialyte, Abbott Laboratories, Abbott Park, Illinois; and Pediatric Electrolyte, PendoPharm, Mont-Royal, Quebec, Canada.

tration of sodium than do most beverages consumed by children. This high-sodium content may make them less palatable than other beverages commonly consumed by children. To eliminate palatability concerns, physicians often recommend solutions such as sports drinks, water, and soda.[10] In fact, 34% of the UK institutions surveyed used a sugar-free cordial as the first-line fluid.[7] The inappropriate use of low-sodium beverages can result in hyponatremia.[11,12] Home flavoring is also commonly recommended, but this can cause severe alterations in electrolyte content and osmolality.[13] In an attempt to improve the palatability of ORSs, some manufacturers have opted to add sucralose. Enfalyte (Mead Johnson Nutritionals, Evansville, Indiana), which does not contain an artificial sweetener, is the provided ORS in many emergency departments, including 31% of Canada's tertiary care pediatric emergency departments (4 of 13) (S.B.F., unpublished data, December 2007). Thus, we performed a randomized crossover trial to determine whether children report taste differences among 3 ORSs—2 that were sweetened with sucralose (Pedialyte [Abbott Laboratories, Abbott Park, Illinois] and Pediatric Electrolyte [PendoPharm, Mont-Royal, Quebec, Canada]) and 1 that was rice based (Enfalyte).

METHODS

STUDY DESIGN AND PARTICIPANTS

A 3-treatment, 3-period, randomized, blinded crossover trial was conducted in the emergency department of The Hospital for Sick Children, Toronto, Ontario, Canada. All presenting children were evaluated for eligibility between May 20, 2008, and June 20, 2008. Eligible patients were aged 5 to 10 years and had a wide range of presenting concerns, such as rash, fever, and minor soft-tissue injuries. Caregivers and participants had to have acceptable command of the English language. Children were excluded from the study if they were dehydrated, were not allowed food or liquid by mouth, or had an episode of vomiting or diarrhea on the day of presentation. Additional exclusion criteria were recent head trauma, abdominal pain, rhinorrhea, and cough. These criteria were selected to maximize the probability of unaltered taste perception because upper respiratory and gastrointestinal tract symptoms can alter taste perception, thereby affecting outcome assessment.[14] After eligibility screening, written informed consent was obtained from parents and assent from children. This study was approved by the research ethics board of The Hospital for Sick Children.

INTERVENTION

All the screening procedures, solution administration, and outcome assessments were performed by a single trained research assistant (D.C.). Eligible participants were randomly assigned to receive 1 of 6 possible tasting sequences (**Figure 1** and **Figure 2**). After an initial 30-minute nothing-by-mouth period, children were instructed to drink as much of each room temperature solution as they desired during the subsequent 15 minutes. Immediately after each ORS was consumed, children rated taste by marking a point on a 100-mm visual analog scale with facial hedonic features (**Figure 3**).[15-18] Between tastings, the children consumed 2 unsalted crackers (Premium Plus; Kraft Canada Inc, Don Mills, Ontario) followed by 3 to 5 oz of water to remove any residual taste[15,17,19] and then waited an additional 5 minutes before tasting the next ORS. After consuming the final ORS, participants were asked which ORS tasted best. The study was completed without interruption while children were waiting to be seen by a physician.

RANDOMIZATION AND BLINDING

The randomization schedule was prepared by The Hospital for Sick Children's research support pharmacy using blocks of 6 within which the 6 treatment sequences were randomly ordered with 1:1:1 randomization to ensure that approximately equal numbers of participants tasted each solution first. An independent pharmacy team member created the randomization sequence using a computerized pseudorandom number generator, allowing all investigators, research assistants, and statisticians to remain blinded until data analysis was complete.

All 3 solutions were used in the commercially available fruit-flavored formulations. The hospital's research support pharmacy repackaged all the solutions into consecutively numbered, identical-appearing 250-mL opaque bottles along with opaque straws. Color matching was performed by our re-

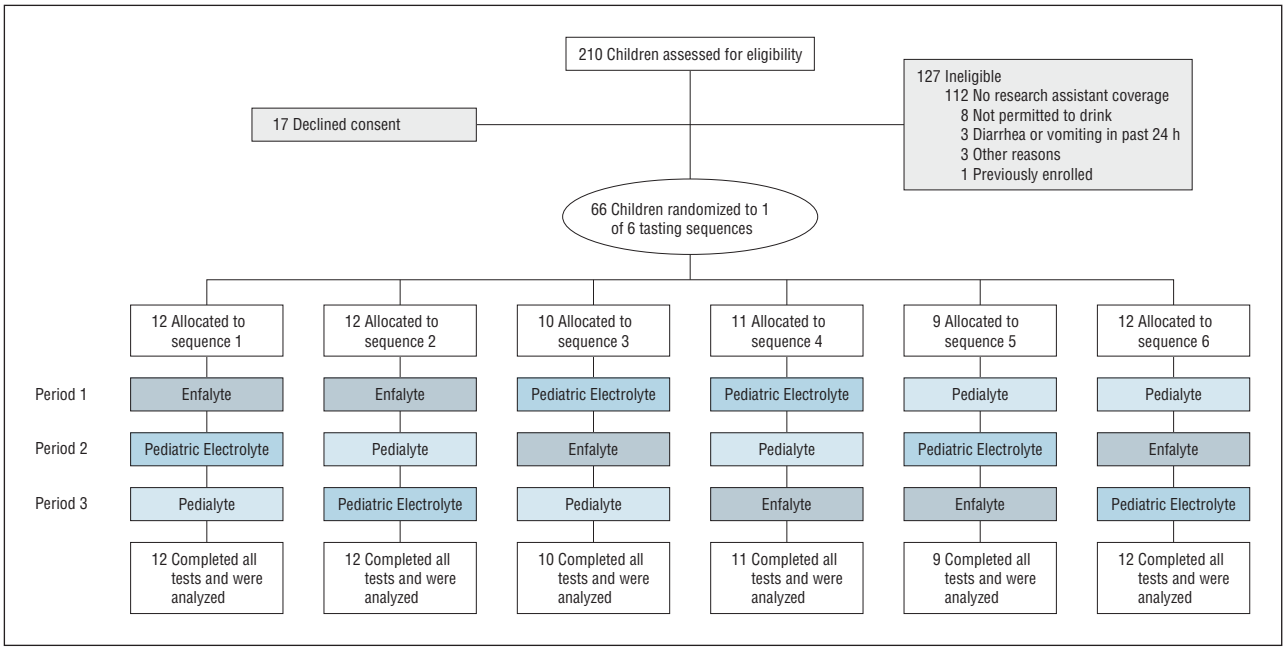

Figure 2. Participant flow in this randomized crossover trial evaluating the taste of 3 oral rehydration solutions. Enfalyte manufactured by Mead Johnson Nutritionals, Evansville, Indiana; Pedialyte, Abbott Laboratories, Abbott Park, Illinois; and Pediatric Electrolyte, PendoPharm, Mont-Royal, Quebec, Canada.

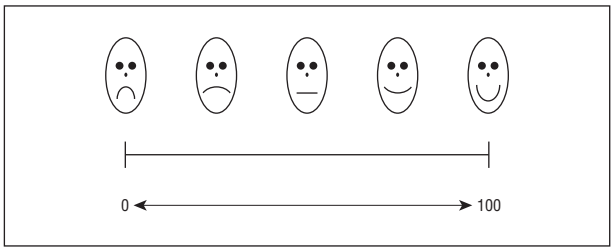

Figure 3. The 100-mm visual analog scale incorporating facial hedonic features used to evaluate taste: 0 indicates the worst score, 100 the best.

search support pharmacy in case of accidental visualization of the solutions by participants. Taste testing was then conducted to determine the shelf life of the repackaged products. Based on this process, it was determined that all experimental solutions must be kept refrigerated and administered within 48 hours of preparation as per the manufacturers' instructions owing to taste alterations that were detected when solutions were consumed beyond that time point.

PRIMARY AND OTHER OUTCOMES

The primary outcome was taste as reported on a visual analog scale with facial hedonic features. After drinking each fluid, children indicated their taste rating by marking a point on a 100-mm line, with 0 indicating the worst possible taste and 100 the best taste. The line was accompanied by 5 drawings of facial expressions indicating bad to good taste (Figure 3). This scale has been used previously to test the palatability of antibiotics[15,16] and activated charcoal[17] in children and adolescents and is preferred to spontaneous verbal judgments because it confers a standardized way to record taste preferences.[18] The research assistant (D.C.) asked children to mark a point on the taste scale provided after the consumption of each experimental liquid. We had 3 secondary outcome measures. First, the volume of each ORS consumed during each 15-minute period. Second, after each period, we asked the child, "If you felt sick in your tummy and this liquid could make you feel better, would you drink it again?" The outcomes of volume and willingness to consume again were evaluated 15 minutes after each tasting period. After the third tasting period, we asked all the participants, "Now that you have tasted 3 liquids, which one of these liquids do you think tastes best?" This allowed us to determine which liquid was preferred by the most children.

Table 1. Characteristics of the Study Solutions[a]

Characteristic	Enfalyte	Pediatric Electrolyte	Pedialyte
Cost, $/L	13.19	3.49	5.99
Sodium, mEq/L	50	45	45
Potassium, mEq/L	25	20	20
Chloride, mEq/L	45	35	35
Citrate, mEq/L	34	10	10
Rice syrup solid, g/dL	3	0	0
Dextrose, g/dL	0	2	2.5
Fructose, g/dL	0	0.5	0
Sucralose, mg/dL	0	37.4	40
Osmolality, mOsm/kg	170	250	250

[a] Enfalyte is manufactured by Mead Johnson Nutritionals, Evansville, Indiana; Pedialyte, Abbott Laboratories, Abbott Park, Illinois; and Pediatric Electrolyte, PendoPharm, Mont-Royal, Quebec, Canada.

SAMPLE SIZE

We sought to compare 3 oral solutions, each with the other (Pedialyte vs Enfalyte, Pedialyte vs Pediatric Electrolyte, and Pediatric Electrolyte vs Enfalyte) (**Table 1**), using 3 tests of statistical significance. We multiplied *P* values by 3 (a Bonferroni correction) to keep the overall type I error proportion at .05.[20] We chose a 10-mm taste score difference as clinically important,[15] assumed that the SD of the score would be 25 mm based on previous studies,[15,17] and assumed a within-child taste score correlation of 0.5. Setting power to 0.9 and type I 2-sided error at 0.05/3=0.017, we estimated a sample size of 66.

Table 2. Baseline Characteristics of the 66 Study Participants

Characteristic	Enfalyte First Group[a] (n=24)	Pediatric Electrolyte First Group[a] (n=21)	Pedialyte First Group[a] (n=21)
Age, mean (SD), y	7.6 (1.6)	7.8 (1.6)	8.2 (1.6)
Weight, mean (SD), kg	26.0 (8.0)	29.6 (6.9)	30.7 (8.3)
Male sex, No. (%)	11 (46)	12 (57)	9 (43)
Heart rate, mean (SD), beats/min	92 (12.7)	90 (18.7)	90 (11.4)
Respiratory rate, mean (SD), breaths/min	21 (2.5)	21 (3.0)	21 (2.9)
Temperature, mean (SD), °C	36.8 (0.4)	36.8 (0.6)	36.7 (0.3)
CTAS score, mean (SD)	3.4 (0.5)	3.5 (0.6)	3.6 (0.5)
Medication use in preceding 24 h, No. (%)	14 (58)	8 (38)	8 (38)

Abbreviation: CTAS, Canadian Triage and Acuity Scale.[25]
[a]Enfalyte is manufactured by Mead Johnson Nutritionals, Evansville, Indiana; Pedialyte, Abbott Laboratories, Abbott Park, Illinois; and Pediatric Electrolyte, PendoPharm, Mont-Royal, Quebec, Canada.

STATISTICAL ANALYSIS

All the primary analyses were conducted under the intent-to-treat principle. We selected a crossover design to allow us to use the patients as their own controls. Because within-patient variation is less than between-patient variation, the study design required a smaller sample size than had a parallel design been used. However, crossover designs may result in carryover effects, defined as the effect that the treatment (taste rating and volume consumed) from the earlier period (period 1 or 2) has on the response in a subsequent period (period 2 or 3).[21] In this study, we evaluated the carryover effect between periods 1 and 2 and between periods 2 and 3. We used repeated-measures analysis of variance to analyze the data for the 2 continuous outcomes of taste score and solution volume consumed to determine whether a significant carryover effect was present.[22,23] Because a significant carryover effect was detected, we provide the data with and without adjusting for the carryover effect because adjusting for such an effect in this design could be problematic.[24] All repeated-measures analyses are adjusted for period and use within- and between-subject data from all the periods. We also estimated mean differences in outcome scores among the 3 solutions. The secondary outcome of willingness to consume each liquid again was analyzed using generalized estimating equations to analyze repeated measures for categorical variables and was adjusted for period using between- and within-subject data. Because the carryover effect was significant, the data are presented with and without adjustment for this effect. The outcome of favorite liquid was evaluated using a logistic regression using a polychotomous outcome adjusted for sequence.

RESULTS

Of the 210 children screened, 83 met the eligibility criteria, and of those, 66 agreed to participate and were enrolled in the trial; all were randomized (Figure 2). Mean age varied across the 3 groups, from 7.6 to 8.2 years; mean weight varied from 26 to 31 kg; and the proportion of boys varied from 43% to 57% (**Table 2**).[25] Temperature, acuity score, and heart and respiratory rates differed little among the groups. Use of medication in the preceding 24 hours ranged from 38% to 58%. Children who were eligible but did not consent to participate in the study did not differ from children who were enrolled in the study. **Table 3** lists the chief concerns of children who were enrolled. All 66 participants completed all the stages of the study.

Table 3. Chief Concerns of the 66 Enrolled Children

Chief Concern	Children, No.
Extremity pain/injury	30
Skin problem	8
Laceration	6
Fever	4
Ear problem	3
Eye problem	3
Mouth/nose problem	3
Other[a]	9

[a]Genitourinary problem (n=2), foreign body (n=2), headache (n=2), syncope (n=2), and psychiatric disorder (n=1).

PRIMARY OUTCOME

Analysis of the primary outcome, the taste score, revealed evidence of a significant carryover effect ($P=.03$) that was greatest from Enfalyte to Pedialyte ($P=.008$). The taste scores, whether adjusted or not for the carryover effect, differed significantly between solutions ($P<.001$ for both) (**Table 4** and **Figure 4**). When Enfalyte was compared with Pediatric Electrolyte (–29 mm adjusted for carryover effect), and Pedialyte (–36 mm adjusted for carryover effect) it scored significantly lower (**Table 5**). The difference between Pedialyte and Pediatric Electrolyte was small (8 mm) and not statistically significant.

OTHER OUTCOMES

Regarding the volume of solution consumed, no carryover effect was detected ($P=.19$), and the differences in the consumption did not reach significance ($P=.44$) (Table 4). With respect to willingness to drink the solution again, there were differences when Enfalyte was compared with Pedialyte (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.25 to 0.57) and with Pediatric Electrolyte (0.22; 0.11-0.46). However, a carryover effect was detected ($P=.02$). After adjustment for the carryover effect, the differences narrowed slightly: Enfalyte to Pedialyte (OR, 0.51; 95% CI, 0.32- 0.81) and Enfalyte to Pediatric

Table 4. Measures of Palatability

Rehydration Solution[a]	Taste Score, Mean (SD), mm		Volume of Solution Consumed, Mean (SD), mL	Would Drink the Solution Again, No. (%)	Solution Tastes the Best, No. (%)
	Unadjusted[b]	Adjusted[c]			
Enfalyte	23 (8)	28 (8)	15.2 (7.2)	26 (39)	5 (8)
Pediatric Electrolyte	58 (8)	56 (8)	16.8 (7.2)	48 (73)	26 (39)
Pedialyte	65 (8)	64 (8)	22.0 (7.4)	47 (71)	35 (53)

[a] Enfalyte is manufactured by Mead Johnson Nutritionals, Evansville, Indiana; Pedialyte, Abbott Laboratories, Abbott Park, Illinois; and Pediatric Electrolyte, PendoPharm, Mont-Royal, Quebec, Canada.
[b] Unadjusted mean taste scores are adjusted for period using within- and between-subject data from all the periods. They are not, however, adjusted for the carryover effect.
[c] Adjusted mean taste scores are adjusted for carryover effects and period using within- and between-subject data from all the periods.

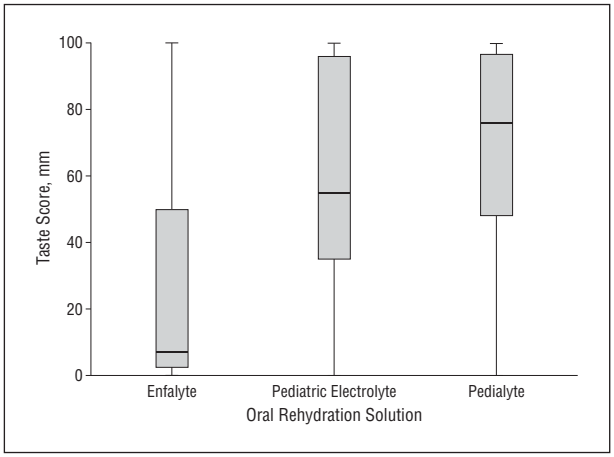

Figure 4. Box plot of the taste scores, unadjusted, for each of the 3 solutions—Enfalyte (Mead Johnson Nutritionals, Evansville, Indiana), Pedialyte (Abbott Laboratories, Abbott Park, Illinois), and Pediatric Electrolyte, (PendoPharm, Mont-Royal, Quebec, Canada). The horizontal line in the middle of each box indicates the median; the top and bottom of the box, quartile boundaries; and the vertical lines, minimum and maximum values within 1.5 times the interquartile range of the quartile boundary.

Electrolyte (0.33; 0.16-0.69). When the carryover effect is left out of the model, children are more willing to consume Pediatric Electrolyte again compared with Pedialyte (OR, 1.69; 95% CI, 1.11-2.59). However, when the carryover effect is included, the OR is no longer significant (OR, 1.54; 95% CI, 1.00-2.26).

Significant differences were noted regarding the best-tasting solution, with Pedialyte selected by 35 of 66 children (53%), Pediatric Electrolyte by 26 of 66 children (39%), and Enfalyte by 5 of 66 children (8%) ($P < .001$). The sequence effect was not significant ($P = .36$). The OR of choosing Pedialyte compared with Enfalyte was 12.3 (95% CI, 4.9-31.0) and compared with Pediatric Electrolyte was 0.78 (0.44-1.4). Pediatric Electrolyte was preferred to Enfalyte (OR, 15.9; 95% CI, 6.0-41.7). No adverse events were reported.

COMMENT

The results of this study suggest that Pedialyte and Pediatric Electrolyte fruit-flavored solutions are significantly better tasting than Enfalyte. However, it remains to be seen whether the observed differences in palatability have a role in improving health outcomes.

Table 5. Taste Score Differences (Unadjusted for Carryover Effects) Among Solutions[a]

Reference Solution[b]	Taste Score Difference, Mean (95% CI), mm		
	Enfalyte	Pediatric Electrolyte	Pedialyte
Enfalyte	0	35 (19 to 51)	42 (26 to 58)
Pediatric Electrolyte	−35 (−51 to −19)	0	7 (−9 to 23)
Pedialyte	−42 (−58 to −26)	−7 (−23 to 9)	0

Abbreviation: CI, confidence interval.
[a] Positive values indicate a higher taste score.
[b] Enfalyte is manufactured by Mead Johnson Nutritionals, Evansville, Indiana; Pedialyte, Abbott Laboratories, Abbott Park, Illinois; and Pediatric Electrolyte, PendoPharm, Mont-Royal, Quebec, Canada.

Given that the 3 tested solutions have similar content and that the better-tasting sucralose solutions cost less, perhaps they should be recommended as initial therapy.

The frequent use of cereal-based ORSs using carbohydrates such as rice starch or wheat may occur because of the perception that they are superior to traditional ORSs. This theoretical benefit is based on their ability to reduce diarrhea by adding more substrate to the gut lumen without increasing osmolality, thereby providing additional glucose molecules for glucose-mediated absorption. Although cereal-based ORSs are of mild benefit compared with glucose-based ORSs when administered to children with cholera diarrhea, a meta-analysis found that the effect of cereal-based ORSs in children with acute noncholera diarrhea was mild and without significance (−4.3 mL of stool/kg/d; 95% CI, −9.4 to 0.8 mL of stool/kg/d).[26] The use of rice-based ORSs also does not reduce the need for intravenous rehydration compared with standard ORSs.[27] In contrast, a meta-analysis[28] of 16 trials on the use of reduced-osmolarity ORSs without a rice base showed a reduction in the proportion of children requiring unscheduled intravenous fluid infusions. The volume of stool output and the frequency of vomiting were also reduced compared with those of standard ORSs.

The lack of a significant difference in volumes consumed should not be construed as implying that the taste difference does not translate into increased volume consumed. In this study, we did not encourage children to

drink large volumes because that might have increased the carryover effect; children who are less hungry and thirsty may have rated solutions consumed at the end of the study less favorably. The children evaluated were not dehydrated, and they simply drank as much as they desired; nevertheless, intake was greater for the sucralose-based solutions.

The provision of ORSs for home use by primary care physicians can reduce the need for unscheduled follow-up visits by up to 37%. The present study, however, did not evaluate the effect of ORS taste on clinical efficacy in children who are dehydrated. We cannot conclusively conclude that the better-tasting solutions are the best for oral rehydration. In fact, even the best-tasting solutions would be voluntarily consumed again by less than half of the participants. Thus, it is possible that none of the ORSs evaluated taste good enough to be recommended as the only solution with which to perform oral rehydration therapy.

A previous comparison of the low-osmolality World Health Organization ORS (sodium = 74 mmol/L) with unflavored Pedialyte (sodium = 45 mmol/L) found that once cost differences were considered, caretakers who prepared and used the low-osmolality World Health Organization ORS were more satisfied than were those who used Pedialyte.[29] The major advantage of commercially prepared ORSs is their availability in preflavored formats using sweeteners that do not significantly alter osmolality. It is the flavoring, sucralose and acesulfame potassium, that theoretically enhances the palatability of, ease of administration of, and, hence, satisfaction with commercially available ORSs. Because unflavored Pedialyte was used and the 10-fold cost difference between the solutions was evaluated, it is not surprising that no difference was detected in ease of administration and that caregivers preferred the World Health Organization ORS. To improve taste, flavoring was added at home by 43% of caregivers.[29] Although very small amounts of flavoring can be added at home without significantly altering the electrolyte composition and osmolality of ORSs, palatability does not improve compared with commercially flavored ORSs.[8]

In this study, we found evidence of substantial carryover effects from one period to the next for the taste outcome score, thereby introducing a potential source of bias in the estimate of the mean taste score differences. We attempted to remove this bias by adjusting for the observed carryover effect. However, such an adjustment produces unbiased estimates only if there is no carryover between periods 2 and 3,[30] which was not the case in this study. We, therefore, analyzed the data without adjusting for the carryover effect, as would be done in a simple randomized trial, and again found that Enfalyte received the lowest taste score compared with the other 2 solutions. For comparison purposes, we also presented the data adjusted for the carryover effect to demonstrate the effect that such an adjustment might have. Future similar trials should attempt to avoid the problem of carryover effects by using a much longer interval between taste sessions. Alternatively, an ordinary randomized trial design might be preferable to a crossover design for studying taste.

This study has several limitations. We chose to evaluate school-aged children because there is no validated taste score for young children who also may have had difficulties complying with the protocol. Although it would have been desirable to have studied children with acute gastroenteritis, most such children evaluated in an emergency department have intractable vomiting, nausea, or abdominal pain. The primary outcome of such a study would not be taste but rather the success of oral rehydration and would require a much larger sample size. Although children with severe dehydration may perceive taste differently and are more likely to drink any solution they are provided, this may not be the case in children with minimal or mild dehydration.[7] Thus, until greater evidence is available, the primary outcome of the present study is important because it may help physicians minimize the use of intravenous rehydration in mildly dehydrated children due to fluid refusal (S.B.F., K.B., and V. Sivabalasundaram, BHSc, V. Bohn, BSc, E. Powell, MD, MPH, and D. Johnson, MD; unpublished data; May 1, 2010).

In conclusion, we found that sucralose-sweetened ORSs, such as Pedialyte and Pediatric Electrolyte, are significantly more palatable than is the rice-based ORS Enfalyte. Whether taste has a role in improving clinical outcomes remains unknown. Given the similar content of the solutions evaluated and that the sucralose solutions are less expensive, perhaps they should be recommended as initial therapy.

Accepted for Publication: February 23, 2010.
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Author Contributions: Dr Freedman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Freedman, Boutis, and Schuh. *Acquisition of data:* Freedman and Cho. *Analysis and interpretation of data:* Freedman, Boutis, Stephens, and Schuh. *Drafting of the manuscript:* Freedman, Boutis, and Stephens. *Critical revision of the manuscript for important intellectual content:* Freedman, Cho, Boutis, Stephens, and Schuh. *Statistical analysis:* Stephens. *Obtained funding:* Freedman, Boutis, and Schuh. *Administrative, technical, and material support:* Cho. *Study supervision:* Freedman and Schuh.
Financial Disclosure: None reported.
Funding/Support: This study was supported by the Paediatric Consultants Partnership's Grant for Creative Professional Activity. PendoPharm, a division of Pharmascience Inc, provided the Pediatric Electrolyte used in this study. The Hospital for Sick Children's Division of Nutrition Services provided the Enfalyte used in this study.
Role of the Sponsor: None of the funding sources played any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

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