Glycine-based oral rehydration solution: Reassessment of safety and efficacy

We evaluated the safety and efficacy of a glycine-based orally administered rehydration solution by comparing it with a standard oral rehydration solution (ORS) without glycine in a randomized double-blind trial in United States infants (age <15 months) given treatment for acute gastroenteritis as inpatients or outpatients. The response to therapy (stool volume and duration of illness) was similar in the two groups, except that in four (13%) of 31 hospitalized infants receiving glycine-ORS hypernatremia developed, (one had symptoms) compared with none of 35 receiving ORS (P <0.04). Among the 77 outpatients there were no differences between the groups. This study demonstrates that glycine-ORS did not provide any therapeutic advantage over standard ORS, and hypernatremia developed in some patients receiving glycine-ORS. We suggest that caution be used with this type of solution until further safety studies have been done. (J PEDIATR 1986;109:795-801)

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Orally administered rehydration solutions containing 50 to 90 mmol/L sodium and 2 gm/L glucose have been shown to be safe and efficacious for treating diarrheal dehydration in both hospitalized and ambulatory infants.[1-3] The physiologic basis for the effectiveness of ORS is the coupled transport of sodium and glucose across the intestinal epithelium.[4] Recent studies in animals and humans have shown that water-soluble organic molecules, such as amino acids, dipeptides, and tripeptides, also enhance the absorption of sodium and water in the small intestine.[5] Two clinical trials in developing countries, one in adults[6] and one in children,[7] have demonstrated that when glycine was added to a glucose-electrolyte ORS, both the duration of diarrhea and stool output were reduced considerably, compared with the use of ORS without glycine. The use of glycine-based ORS, however, has not been evaluated in the developed countries. Therefore, we conducted a double-blind randomized trial to evaluate the safety and efficacy of glycine-ORS compared with ORS containing no glycine.

ORS	Orally administered rehydration solution

The opinions in this article are those of the authors and do not necessarily reflect the views of the Indian Health Service.

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Table I. Composition of oral rehydration solutions

	Solution A (mEq/L)	Solution B (mEq/L)
Sodium	50	50
Potassium	20	20
Chloride	50	50
Citrate*	34	34
Glucose	111	111
Glycine	111	—
Calcium	4	4
Magnesium	4	4
Phosphate	5	5
Osmolality (mOsm/L)	389	278

*11 mmol/L added as citric acid.

METHODS

Patients age 0 to 15 months with acute (7 days or less) watery diarrhea (at least five watery stools per day) were enrolled in the study after informed consent was obtained. The study sites included the United States Public Health Service Indian Hospital, Whiteriver, Arizona, which is the primary health facility for the White Mountain Apache Tribe, the University of Arizona Health Sciences Center, and the Kino Community Hospital, Tucson. A standard physical examination was performed on each patient, and the degree of dehydration was assessed using standard criteria.[8] Patients assessed to have less than 5% dehydration received treatment as outpatients, those assessed to have 7% or more dehydration as inpatients, and patients assessed to have 5% to 7% dehydration either as inpatients or outpatients, depending on the primary physicians' judgment.

Enrolled infants were randomized to one of two groups: Group 1 patients were given an ORS containing 50 mmol/L sodium, 111 mmol/L glycine, and 111 mmol/L glucose (solution A, Glycine-Resol, Wyeth Laboratories; Table I). Group 2 patients received a solution identical in composition to solution A except without glycine (solution B, Resol, Wyeth Laboratories).

Hospitalized patients

Rehydration. Irrespective of the assigned treatment group, severely dehydrated (>9% body weight loss) patients were given intravenous Ringer lactate solution (40 ml/kg) until blood pressure and pulse returned to normal. Following this, rehydration was completed within 4 hours by administering solution A or B, depending on the treatment group to which the infant was randomized. In patients assessed to have mild dehydration (5% to 6% body weight loss) or moderate dehydration (7% to 9% body weight loss), the calculated deficit was replaced within 4 hours with solution A or B alone according to the group to which they were randomized.[9]

Maintenance. After the rehydration period, patients in both groups were given 150 ml/kg of either solution A or B for an additional 24 hours. At the end of 28 hours of hospitalization, all patients were given a full-strength soy-based lactose-free infant formula (Nursoy, Wyeth Laboratories, 150 ml/kg) for the remainder of their hospitalization. In addition, continuing stool losses were replaced on a 1:1 basis with the appropriate ORS. The ORS was discontinued after the infant had no watery stools for 16 continuous hours.

Intake and output measurements. All oral and intravenous intakes were measured and recorded until the diarrhea resolved, as described previously.[9] Stool output was measured using wet and dry diaper weights. Urine output was measured separately from stools in infant boys, using urine bags or urine pads. Volume of vomitus was estimated using wet and dry linen weights. Total body weights were obtained at admission, 4, 8, and 28 hours after admission, and every 24 hours thereafter until discharge.

Antibiotic therapy. Antibiotic therapy was used during hospitalization if, in addition to diarrhea, a concurrent bacterial illness, such as otitis media or pneumonia, was suspected. If shigellosis was suspected clinically or the stool cultures confirmed the presence of *Shigella,* appropriate antibiotics were administered; in the former situation antibiotics were discontinued if bacterial cultures were negative.

Laboratory studies. At the time of hospitalization, the following specimens were obtained from each patient:

1. Whole stool was aspirated using a rectal catheter. One aliquot of stool was used for the identification of bacterial pathogens using standard laboratory techniques.[9] The presence of enterotoxigenic *Escherichia coli* was confirmed by using the DNA hybridization technique.[10] A second aliquot was stored in 10% phosphate-buffered saline solution for identification by enzyme-linked immunosorbent assay of rotavirus antigen, enteric-type adenovirus antigen, and *Clostridium difficile* toxin.[11] A third aliquot was used for direct parasitologic examination.

2. Blood was obtained for determinations of hematocrit; total white blood count with differentials; and serum concentrations of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and total protein. At 8 and 24 hours and at the time of discharge from the study, serum concentrations of sodium, potassium, chloride, bicarbonate, BUN, and total protein were repeated.

Treatment failure. A patient was considered to have a treatment failure if one of the following occurred: (1) the stool output exceeded 80 ml/kg body weight during any 8-hour period after the first 8 hours of hospitalization; (2) there was persistent vomiting (defined as vomiting more than three times during an 8-hour period), necessitating

Table II. Admission characteristics of treatment groups

	Hospitalized patients				Outpatients			
	Group 1* (n = 31)		Group 2† (n = 35)		Group 1* (n = 38)		Group 2† (n = 39)	
	n	%	n	%	n	%	n	%
Age (mo)	5.9 ± 3.1		6.4 ± 3.7		6.9 ± 4.0		7.3 ± 4.3	
Sex (M/F)	19/12		20/15		18/20		18/21	
Mean body weight at admission (kg)	6.5 ± 1.6		6.5 ± 2.0		7.5 ± 1.9		7.7 ± 2.4	
History of vomiting	22	71	20	57	16	42	13	33
Mean days of diarrhea before admission (n)	2.5 ± 1.7		2.9 ± 2.1		2.2 ± 1.5		2.2 ± 1.4	
Antibiotics before admission (n)	5	16	10	29	5	13	4	10
Temperature at admission (°C)	38 ± 1		38± 1		38 ± 1		38 ± 1	
Serum sodium (mmol/L)	142 ± 6		141 ± 5		142 ± 3		141 ± 3	
Serum potassium (mmol/L)	4.3 ± 0.8		4.5 ± 0.9		4.9 ± 0.9		5.2 ± 0.8	
Serum chloride (mmol/L)	112 ± 9		112 ± 8		112 ± 4		111 ± 5	
Serum bicarbonate (mmol/L)	14 ± 5		13 ± 5		17.6 ± 4.4		16.9 ± 4.3	
Total protein (gm/dl)	7.2 ± 1.1		7.4 ± 1.0		6.5 ± 0.7		6.5 ± 0.5	
BUN (mg/dl)	17.5 ± 12.3		17.1 ± 11.0		8.2 ± 4.1		10.5 ± 8.8	
Hematocrit (%)	38.4 ± 5.4		37.8 ± 4.9		NA		NA	
Estimated dehydration:								
Minimal (<5%)	NA		NA		27	71	31	80
Mild (5%-6%)	10	32	16	45	11	29	8	20
Moderate (7%-9%)	20	65	17	49	NA		NA	
Severe	1	3	2	6	NA		NA	
Pathogens identified in stools‡								
Shigella	1	3	4	11	1	3	0	
Campylobacter	1	3	0		2	5	1	3
Aeromonas hydrophila	0		2	6	0		0	
Salmonella	0		0		2	5	0	
Rotavirus	10/28	36	11/30	37	0		1/31	3
Adenovirus	3/28	11	2/30	7	1/28	4	1/31	3

Values denote mean ± SD. No differences between groups were significant.
NA, data not available or not applicable.
*Group 1 received glycine-based ORS.
†Group 2 received ORS without glycine.
‡Bacterial cultures performed for all patients. Number positive/number tested indicated for viral pathogens.

intravenous therapy; (3) diarrheal illness continued for more than 7 days; or (4) the serum sodium concentration exceeded 155 mmol/L after 24 hours of therapy. Patients who were considered to have treatment failures were removed from the study and the primary physician then treated the condition according to his or her clinical judgment.

Outpatients

Outpatients were randomized to receive 200 ml/kg either solution A or solution B for 24 hours. After this, full-strength Nursoy and ORS were given ad libitum, to a maximum of 100 ml/kg/24 hours of each, until the diarrhea stopped. The ORS and Nursoy were dispensed in 8 oz bottles. Patients were seen daily at the clinic or in their homes until the diarrhea stopped. Total body weight was obtained on admission to the study and daily until the diarrhea resolved. During the follow-up clinic or home visits, the quantity of ORS and Nursoy remaining in the bottles since the last visit was measured by one of the staff. If the bottles were not available for inspection, the mother was questioned about the volume of formula and ORS ingested by the infant.

Laboratory studies. Specimens obtained on admission to the study included (1) blood for the determination of serum levels of sodium, potassium, chloride, bicarbonate, BUN, and total protein, and (2) stool for processing as described for hospitalized patients. Twenty-four hours after the initial visit, blood was again obtained for the determination of the above-listed serum values.

Treatment failure. Patients were considered to have treatment failures after 24 hours of therapy if one of the following occurred: (1) the degree of dehydration was

Table III. Features of treatment groups during therapy: Hospitalized patients

	Group 1* (n = 35)	Group 2† (n = 31)	P
Antibiotics during hospitalization	14 (40%)	17 (54%)	
ORS intake 0-4 hr (mL/kg)	75 ± 39	74 ± 27	
ORS intake 5-28 hr (mL/kg)	222 ± 79	196 ± 75	
Total ORS intake during illness (mL/kg)	278 ± 159	278 ± 132	
Soy formula intake during illness (mL/kg)	107 ± 117	112 ± 157	
Total fluid intake during illness (mL/kg)	344 ± 241	341 ± 241	
Stool output 0-4 hr (mL/kg)	18 ± 16	15 ± 15	
Stool output 5-28 hr (mL/kg)	82 ± 62	65 ± 39	
Total stool output during illness (mL/kg)‡	109 ± 96	102 ± 80	
Boys	107 ± 104	95 ± 68	
Girls	112 ± 88	110 ± 94	
Total urine output: boys‡ (mL/kg)	131 ± 84	119 ± 97	
Serum sodium (mmol/L)			
8 Hr after admission	142 ± 5	139 ± 4	.025
28 Hr after admission	144 ± 7	141 ± 3	<0.001
Resolution	142 ± 2	141 ± 3	NS
BUN (mg/dl)			
8 Hr after admission	18.5 ± 8.9	11.3 ± 9.6	.002
28 Hr after admission	19.4 ± 25.8	4.5 ± 2.8	<0.001
Resolution	10.8 ± 2.4	6.5 ± 3.5	<0.001
Duration of diarrhea (hr)	30 ± 21	33 ± 26	
Boys‡	27 ± 18	30 ± 18	
Girls	35 ± 25	36 ± 33	
Percent weight gain			
4 Hr after therapy	2.8 ± 2.1	2.9 ± 2.2	
28 Hr after therapy	6.2 ± 4.4	5.0 ± 3.3	
Resolution	4.6 ± 3.5	4.6 ± 3.5	

Values denote mean ± SD. P values indicated for features statistically significant. All other differences were not statistically significant.
*Group 1 received glycine-based ORS.
†Group 2 received ORS without glycine.
‡N = 19 in group 1 and 20 in group 2.

considered to be 5% or more (by clinical assessment or by weight loss); (2) the serum sodium concentrations exceeded 155 mmol/L at 24 hours after the initial visit; (3) persistent vomiting necessitating hospitalization; or (4) the diarrheal illness continued for more than 7 days.

Statistical methods. Chi-square analysis was used on nominal data except those for which the Fisher exact analysis was indicated (the expected number in any cell was less than 5). A two-tailed t test was performed on interval data with normal distributions and equal variances, and modified appropriately for unequal variances. The Wilcoxon nonparametric test was used when the distribution was not normal.

RESULTS

Hospitalized patients. Sixty-six patients were enrolled in the study, 56 (85%) at the Whiteriver site and 10 (15%) at Tucson. Thirty-one patients were randomized to group 1 and 35 to group 2. Clinical comparison of the groups (Table II) showed no statistically significant differences in admission characteristics. Rotavirus was associated with 36% of the diarrheal illnesses in group 1 and 37% in group 2.

Serum electrolyte values. The mean serum sodium values at 8 and 28 hours after admission were significantly higher in group 1 compared with group 2 (Table III). Similarly, the serum BUN values at 8 and 28 hours and at resolution were higher in patients receiving the glycine-ORS (group 1) than in patients who received ORS without glycine (group 2). There were no differences in the mean serum potassium and bicarbonate values between groups at 8 and 28 hours after hospitalization and at resolution. In four (13%) of the 31 patients in group 1 hypernatremia (serum sodium concentration >150 mmol/L) developed during hospitalization (Table III), compared with none of the patients in group 2 (P <0.04, Fisher exact analysis). Two patients (6%) in the glycine-ORS group had asymptomatic hypernatremia (serum sodium concentration of 160 and 152 mmol/L, respectively) at the time of admission. Similarly, two (6%) patients who received the standard ORS had asymptomatic hypernatremia (serum sodium concentration 150 and 151 mmol/L, respectively) at the time of hospitalization. The illness in all four of these patients resolved uneventfully and their serum sodium values returned to normal at the time of resolution.

Three of the four patients in whom hypernatremia

Table IV. Features of treatment groups during therapy: Outpatients

	Group 1* (n = 38)	Group 2† (n = 39)
Antibiotics during therapy	12 (32%)	13 (33%)
ORS intake first 24 hr (mL/kg)	167 ± 50	165 ± 69
Other intake first 24 hr (mL/kg)	33 ± 33	20 ± 11
Total ORS intake during illness (mL/kg)	264 ± 138	253 ± 140
Soy formula intake during illness (mL/kg)	141 ± 113	182 ± 121
Other fluid intake during illness (mL/kg)	38 ± 32	25 ± 25
Total intake of all fluids (mL/kg)	342 ± 249	396 ± 255
BUN‡ (mg/dL)	11.9	7.2
Weight gain (%)		
24 Hr after therapy	2.5 ± 3.0	2.1 ± 2.8
Resolution	2.3 ± 3.1	1.3 ± 3.0
Duration of diarrhea (days)	2.2 ± 1.5	2.4 ± 1.1

Values denote mean ± SD. No differences between groups were statistically significant unless indicated.
*Group 1 received glycine-based ORS.
†Group 2 received ORS without glycine.
‡P <0.001.

developed during hospitalization had no symptoms; their serum sodium values returned to normal at the time of discharge. These three patients completed the treatment protocol. The fourth child (patient 63), however, had symptoms, and was removed from the study 28 hours after hospitalization (see below). Two of the three patients with asymptomatic hypernatremia were assessed to have mild dehydration at the time of admission (serum sodium values 142 and 145 mmol/L, respectively). Their subsequent respective serum sodium values were 146 and 147 mmol/L at 8 hours after hospitalization, 150 and 150 mmol/L at 28 hours after hospitalization, and 141 and 144 mmol/L at the time their illnesses resolved. The third patient with asymptomatic hypernatremia was assessed to have moderate dehydration at the time of hospitalization (serum sodium concentration 144 mmol/L). His subsequent serum sodium values during hospitalization were 152 mmol/L at 8 hours after admission, 144 mmol/L at 28 hours after admission, and 141 mmol/L at the time of resolution.

Patient 63, with symptomatic hypernatremia, was admitted with a 5-day history of diarrhea and was assessed to have moderate dehydration. He was randomized to the group receiving the glycine-ORS. After the initial 4 hours of rehydration therapy, he continued to manifest signs of dehydration and was given rehydration therapy for an additional 4 hours. At the end of this 8 hours his state of hydration had improved, but his serum sodium value had increased from 140 mmol/L at admission to 154 mmol/L. The treatment protocol was continued with frequent careful monitoring. During the next 24 hours he was noted to become febrile, with a temperature of 39.5° C. His stool output ranged from 8 to 12 ml/kg/hr, and stool pH from 5 to 6. Stool reducing substances were noted to be 1% to 2%. At the end of the first 28 hours of hospitalization, his serum sodium concentration rose to 166 mmol/L, he became extremely irritable, hyperreflexic, and remained febrile; he was removed from the study at this time. He was subsequently given intravenous therapy for 2 days, after which his serum sodium concentration returned to normal within 48 hours and his stool output decreased dramatically. Diarrhea resolved in this patient 2 days later, and he was discharged from the hospital in a normal state of health.

Clinical course of illness. One (3%) patient in group 1 was considered to have a treatment failure (Table III). One (3%) patient in group 2 was also considered a treatment failure, because at 28 hours after admission his stool output exceeded 80 ml/kg/8 hr. At the time of removal from the study, this patient's stool pH was 5 and stool reducing substances were positive at 1%. Among the other 64 patients who successfully completed therapy, there were no statistically significant differences in the intake of fluids, output of stool and urine, weight gained, and duration of diarrhea (Table III).

Outpatients. Seventy-seven patients were enrolled in the study, 51 (66%) at Whiteriver and 26 (34%) at Tucson. Thirty-eight patients were randomized to group 1, and 39 to group 2. There were no statistically significant differences in admission characteristics between the groups (Table II). The mean serum BUN 24 hours after therapy was higher in outpatients who received the glycine-ORS than in those given ORS without glycine (Table IV). All other electrolyte values, amount of fluid intake, and duration of diarrhea were similar between the groups. The percent gain in body weight was similar 24 hours after therapy and at resolution.

One patient in the glycine-ORS group was considered to have treatment failure because of the development of mild dehydration 24 hours after therapy.

DISCUSSION

Our data demonstrate that a glycine-based ORS did not provide any therapeutic advantage over standard ORS, and perhaps even more important, hypernatremia may be a significant hazard with the use of ORS containing glycine in certain populations.

Both of these findings are in contrast to those reported in a recent study performed in Calcutta, where Patra et al.[7] found that small children given the World Health Organization formulation of ORS containing glycine had 50% less stool output and a 30% reduction in the duration of diarrhea. Hypernatremia did not develop in any of the 23 children receiving glycine-ORS. The differences in these two studies can possibly be explained by the differing causes of diarrhea, severity of diarrhea, host responses to diarrheal illness, or study design.

In the Calcutta study of 47 children, only 13 (28%) had rotavirus as the etiologic agent, whereas 13 (28%) had *Vibrio cholerae,* 11 (23%) had enterotoxigenic *E. coli* isolated, and five (11%) had various combinations of these pathogens. In our study, more rotavirus infections were seen and no *V. cholerae* or enterotoxigenic *E. coli* were isolated. Because rotavirus alters the crypt/villus ratio in the small intestine, there may have been more interference with the glucose-facilitated transport mechanism in the U.S. patients. Furthermore, this difference in cause was also reflected in a greater severity of illness, as shown by the mean stool output in the Calcutta study (253 ml/kg stool during the illness in the control children) compared with our study (109 ml/kg stool in the control children). No children were reported to have glucose malabsorption during the Calcutta study, whereas at least two (3%) of our 66 patients were noted to be malabsorbing glucose and had concomitant high stool outputs. In the Calcutta study, patients were allowed to drink a variety of fluids (including human milk) and to take solid foods such as rice during therapy, whereas in our study only ORS was taken during the first 24 hours of the maintenance period and only soy-based formula given additionally after this period. Finally, the Calcutta children were older (average 18 to 19 months of age) than our study children (average 6 months of age).

We can only speculate as to which of these differences were important in producing these divergent results. The development of hypernatremia in our study may have been secondary specifically to glucose malabsorption. As seen in one patient in this study, hypernatremia does not develop in children receiving only ORS if glucose is not absorbed,[12] because sodium is also not absorbed; if the ORS also contains glycine, however, sodium absorption will proceed independent of glucose absorption, and the voluminous stool resulting from the osmotically active unabsorbed glucose will be low in sodium, resulting in the possibility of hypernatremia. Inasmuch as glucose malabsorption is known to occur more frequently (10%) in some populations than in others,[12] this complication may be seen rarely in populations such as those in India and Bangladesh, where glucose malabsorption is infrequent. Unfortunately, we did not routinely evaluate our children for glucose malabsorption, and therefore do not know whether it occurred in the three patients with asymptomatic hypernatremia. The providing of early additional fluids in the Calcutta study could also have prevented significant hypernatremia from developing. It is known that early feeding alone, using either human milk[13] or soy formula[9] or rice-based ORS,[14] may significantly decrease the severity of diarrhea; thus, it is possible that when feeding is not carefully controlled, differences in study outcome may be obscured or exaggerated by the feeding itself.

Although the inpatient group receiving glycine-ORS had significantly higher mean concentrations of serum sodium and BUN during the course of therapy, these values were still within normal limits, and probably reflect only the additional amino acid load and presumed increased sodium absorption.

Two patients in each group who had hypernatremia were successfully treated with ORS. The successful treatment of hypernatremia with standard ORS has been demonstrated previously,[1,15] but has not been demonstrated for glycine-ORS.

Although the glycine-based ORS used by us contained only 50 mmol/L sodium, a glycine-ORS containing 90 mmol/L sodium may have caused hypernatremia in more patients. Hypernatremia may also have been prevented had we used an ORS containing less glucose and glycine or an ORS containing a maltodextrin and glycine, because the latter combination of substrates would have presented less osmotic load to the gut.

In summary, we did not find that a glycine-based ORS resulted in any decrease in stool volume or shortening of diarrheal illness. We did find that hypernatremia developed significantly more often in children taking the glycine-ORS. We therefore urge caution in the use of glycine-ORS until further data regarding its efficacy and safety are available.

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