Alanine-based oral rehydration therapy for infants with acute diarrhea

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Twenty male infants less than 1 year of age with acute diarrhea and dehydration were randomly assigned to a study group and studied in blind fashion in a metabolic unit to assess the efficacy of the addition of 30 mmol/L alanine to the standard World Health Organization (WHO) oral rehydration solution (ORS). Patients were exclusively rehydrated with one of two types of ORS during the first 24 hours of treatment. On the second day, oral feedings were started with a lactose-free formula, and ORS was given to replace stool losses. Body weight, ORS, food intake, vomitus, stool, and urine output were recorded at 6-hour intervals. Blood was drawn at the time of admission, after rehydration, and at 24 and 48 hours of hospitalization to monitor blood gases and electrolytes. Rehydration was satisfactory in both groups of patients. ORS that contained alanine did not reduce the purging rates of the infants compared with those who received standard ORS. Clinically no adverse effect of the alanine-based ORS was observed during hospitalization. None of the patients had significant hypernatremia or hyponatremia, and serum amino acid levels were not altered. These data show that the addition of 30 mmol/L alanine to the standard WHO-ORS produces no further improvement in the outcome of the infants with acute diarrhea compared with those fed the standard WHO-ORS. (J PEDIATR 1991;118:S86-90)

Oral rehydration therapy is now recognized as a major advance in the treatment of acute diarrhea[1]; ORT is a practical and powerful tool for the replacement of fluids,[2] an invaluable public health weapon,[1-3] and one of the least expensive health interventions.[4] The oral rehydration solution recommended by the World Health Organization and the United Nations International Children's Emergency Fund may rehydrate 90% of dehydrated patients, reduce the number of hospital admissions for diarrhea treatment by at least 50%, and reduce diarrhea-associated mortality and limit weight loss when used with appropriate feedings.[4]

However, ORT with the ORS formulations presently available does not reduce the volume, frequency, or duration of diarrhea.[5,6] The acceptance of ORT may thus be limited, because a major concern of the mother and the health worker is to reduce the frequency and volume of the child's stools. Therefore research efforts have been directed to develop improved ORS formulations that would decrease the purging rates while replacing fluids and electrolytes.[7] Basically, two alternative formulations have been studied. Both glucose polymers and amino acids or peptides have been added in varying concentrations.[8-12] Studies conducted in animal models have suggested that glutamine and alanine as well as the dipeptide Ala-Ala enhance water and sodium absorption through the amino acid–dependent cotransport of sodium.[13-16]

ORS	Oral rehydration solution(s)
ORT	Oral rehydration therapy

Recent data in adults and older children with severe secretory diarrhea (caused by *Vibrio cholerae*) showed that ORS with 90 mmol/L alanine and 90 mmol/L glucose was

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Table I. Clinical features of male infants with diarrhea and dehydration

	Control group; WHO-ORS	Study group; WHO-ORS + 30 mmol/L alanine
No. of patients	9	11
Age (mo)	7.1 ± 2.4	6.6 ± 3.4
Weight on admission (kg)	6.4 ± 1.3	7.2 ± 1.9
Weight/length ratio	88.3 ± 11.6	82.6 ± 9.2
Diarrhea before admission (days)	3.6 ± 1.4	2.7 ± 1.4
No. of stools before admission	6.8 ± 3.5	5.9 ± 3.0
Presence of vomiting: no. (%)	5 (56)	10 (91)
Presence of fever: no. (%)	9 (88)	7 (67)
Serum sodium (mEq/L)	128 ± 19	130 ± 10
Serum potassium (mEq/L)	4.6 ± 1.7	4.6 ± 0.8
Blood pH	7.29 ± 0.13	7.28 ± 0.10
Blood HCO_3 (mEq/L)	11.9 ± 6.1	12.2 ± 5.3

Table II. Metabolic balance of male infants with diarrhea

	Study group; ORS + 30 mmol/L alanine	Control group; WHO-ORS
Stool output, gm/kg, 0-6 hr	30.4 ± 22.3	17.9 ± 8.0
Stool output, gm/kg, 6-12 hr	24.8 ± 19.1	15.7 ± 10.2
Stool output, gm/kg, 12-24 hr	27.8 ± 13.6	25.1 ± 9.2
Total stool output, gm/kg, day 1	83.0 ± 46.7	54.3 ± 29.3
Total stool output, gm/kg, day 2	37.1 ± 20	36.7 ± 18.8
ORS intake, ml/kg, 0-6 hr	74.9 ± 55	55.0 ± 32
ORS intake, ml/kg, 6-12 hr	35.0 ± 32	44.0 ± 24
ORS intake, ml/kg, 12-24 hr	72.0 ± 36	83.0 ± 32
Total ORS intake, ml/kg, day 1	185.7 ± 58.1	157.6 ± 76.5
Total ORS intake, ml/kg, day 2	57.8 ± 25	57.3 ± 23
Weight gain day 1 (gm)	102 ± 231	76 ± 187
Weight gain day 2 (gm)	115 ± 215	153 ± 48
Weight gain day 7 (gm)	118 ± 104	100 ± 144

Data are expressed as mean ± SD. Differences were not significant.

absorbed more efficiently and was associated with a 40% reduction of stool output as compared with the standard WHO solution.[17] However, the solution administered to these patients was hypertonic and contained large quantities of alanine. Alanine at a concentration of 30 mmol/L has been shown to be capable of maximal enhancement of water and sodium transport in experimental studies.[14-15] Alanine is very expensive and large quantities could be toxic,[18-19] so we tested the effectiveness of a 30 mmol/L alanine-based ORS in the treatment of infants with acute diarrhea.

PATIENTS AND METHODS

A blinded, randomized study of the effectiveness of alanine-based ORS compared with the standard WHO-ORS was carried out in male infants less than 12 months of age with a history of 5 or fewer days of watery diarrhea and with overt clinical signs of dehydration. None of the patients studied was solely breast fed or had any serious concurrent illness such as pneumonia, meningitis, or sepsis. The patients had no clinical signs of severe malnutrition (body weight deficit for length less than 30%), ileus, or intestinal obstruction. The patients selected for this study were admitted to the Fima Lifshitz Metabolic Unit of the Hospital de Pediatria Professor Edgar Santos da Universidade Federal da Bahia.

The patients were weighed and placed on metabolic beds with bags for separate collection of stools and urine. All patients were given ORS, and only one infant required additional intravenous therapy for the first 4 hours of treatment. In general, the amount of fluid given was calculated to replace the estimated hydration deficit and the continuing stool losses. During the initial rehydration phase, ORS was given at a rate of 100 ml/kg/hr for the first 4 hours of treatment. Thereafter ORS for the first day of treatment was calculated to replace continuing stool losses and to provide basal maintenance requirements for age.

The patients were given ORS exclusively during the initial 24 hours of oral rehydration treatment. On the second day they were fed a lactose-free, cow milk–based formula. ORS and water were offered in quantities sufficient to replace stool losses. Body weight, fluid intake, and stool and urine output were measured, and vital signs were summarized every 6 hours until the patient was discharged from the study. After 48 hours of observation, the patients were discharged and followed clinically. On day 7, after they were weighed, they resumed their customary diet.

Two types of ORS were used for this study. Nine patients received the standard WHO-ORS (control group), and 11 patients received the ORS containing alanine (study group). The alanine ORS differed from the standard WHO-ORS only by the addition of 30 mmol/L alanine. Thus the total osmolality of both solutions was slightly different (310 versus 340 mmol/L). The salt contents of the control and the study formulations were identical; that is, sodium chloride (90 mmol/L), potassium chloride (20 mmol/L), and trisodium citrate dihydrate (10 mmol/L). Packets of the control and study ORS were provided by the hospital pharmacy. They were identical in appearance and numbered sequentially according to a randomization chart coded by the pharmacy.

At the time of admission, stool specimens obtained with rectal catheters were searched for parasites. Blood samples

Table III. Serum amino acid levels of male infants with acute diarrhea during treatment for dehydration

	Study group; ORS + 30 mmol/L alanine		Control group; WHO-ORS	
	Basal	Day 2	Basal	Day 2
Threonine	111.0 ± 2.1	166.0 ± 53.7	134.0 ± 2	193.5 ± 81.5
Valine	249.6 ± 34.9	229.9 ± 43.0	193.6 ± 25.6	250.8 ± 48.9
Methionine	29.6 ± 6.2	29.6 ± 6.2	41.6 ± 15.1	35.8 ± 9.4
Isoleucine	65.3 ± 7.3	66.8 ± 11.3	55.0 ± 8.3	78.8 ± 16.3
Leucine	243.9 ± 68.9	187.9 ± 49.1	156.6 ± 24.2	217.2 ± 44.2
Phenylalanine	137.6 ± 14.7	120.1 ± 25.1	123.4 ± 18.3	127.6 ± 18.8
Tryptophan	32.0 ± 4.1	24.4 ± 2.3	27.6 ± 5.7	25.2 ± 8.1
Lysine	218.1 ± 17.9	288.1 ± 74.7	229.4 ± 33.8	303.0 ± 54.7
Histidine	116.7 ± 16.6	87.9 ± 5.2	102.0 ± 16.2	112.6 ± 13.8
Arginine	125.7 ± 18.6	105.7 ± 11.9	136.3 ± 24.5	203.0 ± 48.5
Taurine	185.0 ± 25.2	200.5 ± 22.9	161.6 ± 22.5	154.5 ± 21.9
Serine	262.5 ± 20.9	290.4 ± 29.3	256.9 ± 38.2	325.0 ± 47.0
Glutamic acid and asparagine	268.1 ± 35.5	256.6 ± 25.9	235.6 ± 36.4	296.0 ± 57.5
Glutamine	218.7 ± 26.6	235.8 ± 235.8	239.4 ± 61.5	277.5 ± 59.4
Proline	215.8 ± 23.4	224.2 ± 15.6	208.1 ± 32.1	299.6 ± 32.8
Glycine	369.9 ± 37.4	430.3 ± 85.1	337.7 ± 52.9	393.0 ± 52.7
Alanine	530.3 ± 84.5	563.7 ± 59.1	451.9 ± 87.3	556.2 ± 113.1
Citruline	12.7 ± 3.0	8.9 ± 1.4	7.2 ± 1.2	13.0 ± 2.9
AAIB	21.1 ± 3.8	21.7 ± 2.4	20.3 ± 5.0	20.2 ± 3.6
Tyrosine	68.8 ± 8.2	89.7 ± 14.5	57.6 ± 7.1	104.2 ± 28.9
β-Alanine	7.1 ± 0.8	7.8 ± 0.9	5.9 ± 0.6	4.5 ± 1.1
β-ABA	9.1 ± 1.4	5.1 ± 1.0	7.4 ± 2.6	5.5 ± 1.4
Ornithine	94.7 ± 18.9	82.7 ± 11.1	75.1 ± 18.8	90.4 ± 23.2
3-MeHistidine	3.9 ± 0.3	3.1 ± 0.5	4.0 ± 0.7	3.0 ± 0.4
Essential*	1251.8 ± 164.5	1218.8 ± 239.3	1109.9 ± 173.3	1033.1 ± 337
Nonessential*	2248.9 ± 173.9	1760.0 ± 501.7	2073 ± 231.7	2405.2 ± 207
E/NE	0.351 ± 0.016	0.321 ± 0.017	0.342 ± 0.015	0.362 ± 0.016

Data are expressed as mean ± SEM.
AAIB, α-Aminoisobutyric acid; *β-ABA*, β-aminoisobutyric acid; *E/NE*, ratios of sums of essential to nonessential amino acids.
*Sum of these amino acids.

were collected at the time of admission (hour 0), after the rehydration phase (at about 4 hours), and at 24 and 48 hours after the treatment was started. Body weight (in grams), stool output and vomitus (in grams per kilogram body weight), and the intake of ORS and milk formula (in grams per kilogram body weight) were also evaluated at those times. Serum sodium, potassium, and blood gases were measured with the Na/K Analyses IL 501 System and pH/Blood Gases Analyser IL System 1304 (Instrumentation Laboratory, Lexington, Mass.). Plasma amino acids levels were determined at the time of admission, and at the end of the study, they were measured from venous blood samples. Plasma was treated with Seraprep (Pickering Laboratories, Mountain View, Calif.), and the supernatant was analyzed by high-performance liquid chromatography.[20] Statistical analysis of the clinical and biochemical variables was performed by *t* tests.

In all instances informed consent was signed by the parents or legal guardians of each child. The protocol was approved by the North Shore University Hospital Research Committee, the ethical review committee of the Hospital Professor Edgard Santos, Universidade Federal da Bahia, and the Regional Medical Board.

RESULTS

The two patient groups were comparable (Table I). However, more patients in the study population had a history of vomiting before admission. The patients in both groups had mild hyponatremia and metabolic acidosis.

The addition of alanine to the WHO-ORS did not improve the outcome of the patients (Table II). No decrease was observed in the purging rate of the infants, and the amount of vomitus and number of vomiting episodes did not differ in the two groups. The amount of fluids needed to correct dehydration and to replace fluid losses was not modified by the addition of alanine. In all instances diarrhea improved after 24 hours of oral rehydration, regardless of the ORS employed. During the second day of treatment,

when lactose-free feedings were given, the severity of the diarrhea lessened; however, all patients continued to have mild to moderate stool losses.

The serum electrolytes, blood pH, and bicarbonate levels of the patients revealed no advantage with the alanine ORS. However, the use of amino acid–supplemented ORS did not produce any negative effects. The patients did not experience hypernatremia or hyponatremia, nor did hypokalemia occur (potassium less than 3 mEq/L).

The addition of 30 mmol/L alanine to ORS did not alter serum amino acid levels (Table III). Serum alanine concentrations were within the normal range at the time the infants were admitted to the study, and rehydration with an alanine ORS did not elevate serum alanine levels after 48 hours of study. Similarly, other amino acids were not affected by the presence of alanine in the ORS. The balance between essential and nonessential amino acids was also unaltered by the addition of alanine.

DISCUSSION

Our results show that the addition of 30 mmol/L alanine to the standard WHO-ORS does not improve the outcome for infants with acute diarrhea. These data differ from those obtained with the use of ORS containing 90 mmol/L alanine in older patients with severe secretory diarrhea caused by cholera or enterotoxigenic *Escherichia coli*. However, they agree with other studies showing that "improved ORS" formulations containing other amino acids have not improved the outcome for patients compared with the standard ORS treatment.[7] Results from six studies in children less than 3 years of age with acute diarrhea similar to that seen in our patients (including diarrhea associated with rotavirus) showed that the addition of glycine or glycylglycine to a glucose ORS had no consistent beneficial effect on the stool output, intake of ORS, or duration of diarrhea.[10, 21, 22]

The use of specific amino acids to supplement ORS is based on experimental evidence that these are highly effective in promoting sodium and water transport across the intestinal brush border membrane.[12] Amino acids may improve water and sodium transport by mechanisms distinct from those of glucose, suggesting that these may provide an additional benefit when combined with a carbohydrate in an ORS.[13-16] This enhancement might be associated with a decreased mucosa-to-lumen water outflow and an accelerated exit of glucose and amino acid through the basolateral membrane of the enterocyte.[14]

However, in clinical situations the theoretic physiologic benefits of an amino acid–supplemented ORS may not be detectable. Alanine enhances jejunal sodium and water transport;[13] however, there may be a diminished brush border membrane sodium-dependent L-alanine transport in acute viral gastroenteritis,[23] so there may be limitations to the enhancement of this mechanism in acute diarrhea in children. Additionally, the expense of alanine calls into question the cost-effectiveness of supplementing the ORS with large quantities of this amino acid to improve its efficacy.

Although a larger amount of alanine may have a positive role in the reduction of purging rates in severe diarrhea,[17] other additives like those derived from rice are more readily available worldwide and may be effective in improving the efficacy of ORS at a very low cost. Several rice-based ORS have been employed for the treatment of infants with diarrhea throughout the world.[10, 11, 24-32] These rice-based formulations have had a performance comparable to or better than that of the WHO-ORS. Glucose polymers derived from corn have also been used as substitutes for glucose in the treatment of acute diarrhea, since these allow for a lower osmolality of the feeding.[33] Low osmolality solutions enhance intestinal water transport and may therefore improve the efficacy of the ORS.[34-35]

CONCLUSIONS

In designing an ORS that may be effective in the treatment of dehydration and may reduce the purging rates of infants with diarrhea, the data obtained from experimental studies showing improved water and sodium transport[13-16, 34-38] need to be evaluated clinically. Data derived from older patients with severe secretory diarrhea or from experimental models of different types of diarrhea should not be extrapolated to the infant with gastroenteritis without a clinical trial. Finally, the cost-effectiveness and worldwide availability of specific additives need to be considered before recommendations are made for widespread use.

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