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Hydrolyzed lactalbumin-based oral rehydration solution for acute diarrhoea in infants

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The addition of different organic substrates to standard glucose oral rehydration solution (G-ORS) has been shown to improve the intestinal absorption of sodium and water, and thereby decrease stool losses. Therefore, we evaluated, in infants with acute diarrhoea, the safety and efficacy of three oral rehydration solutions (ORS) which had the same concentrations of electrolytes (with sodium 60 mmol/l) but different substrates of proteins and carbohydrates. One solution (LAD-ORS) contained hydrolyzed lactalbumin (LAD) with maltodextrin and sucrose, a second (MS-ORS) was identical but without LAD and a third (G-ORS) was standard glucose ORS. The three solutions were compared in a double-blind, randomized trial in 74 hospitalized well-nourished children in Panama and the United States. All three oral rehydration solutions were equally efficacious and safe in these children, 54% of whom were infected with rotavirus. There was no suggestion that hydrolyzed lactalbumin or maltodextrin provided any advantage over glucose-ORS in terms of stool output or in duration of diarrhoea. We conclude that all three solutions are efficacious in the therapy of acute diarrhoea in infants. □ *Diarrhoea, dehydration, oral rehydration solution*

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The safety and efficacy of oral rehydration solutions (ORS) for treating both ambulatory and hospitalized infants with diarrhoea accompanied by dehydration have been well documented (1–4). The physiological basis for the effectiveness of standard ORS has also been described previously (5, 6). Additionally, studies in animals and humans have shown that water soluble organic molecules, such as amino acids (glycine), dipeptides and tripeptides, enhance the absorption of sodium and water in the small intestine (7, 8). In one study (9), however, it was demonstrated that a glycine-based ORS did not provide any therapeutic advantage over standard ORS and that, moreover, hypernatraemia developed in some patients who received the glycine-based ORS. Other studies (10–12) have shown that, compared to standard ORS, an ORS containing cooked rice powder significantly reduced the volume of diarrhoeal stools and the duration of illness in children with acute watery diarrhoea. Studies in older children and adults with cholera have also found that an alanine-based ORS also significantly reduced stool output (13). Further studies (14) have shown that hydrolyzed whey protein containing amino acids of different amounts improved sodium absorption more than an equivalent mixture of amino acids. Therefore, we conducted a randomized, double-blind trial to evaluate the safety and efficacy of a hydrolyzed whey protein-based (LAD) ORS which also contained maltodextrin. LAD-ORS was compared to a second solution containing maltodextrin without LAD and a third, standard ORS. Each of the three solutions contained the same concentrations of electrolytes.

Materials and methods

Patients

The study population consisted of infants of both sexes less than 15 months of age, who presented with acute watery diarrhoea of less than seven days duration, and who were passing at least five watery stools in the 24 h prior to admission. All were judged to be significantly dehydrated, 5% or more on clinical grounds (15), and requiring hospitalization. All were well-nourished children with length- and weight-for-age above the third percentile (according to standards published by the United States Center for Health Statistics, 1976) (16). Informed consent was obtained from the parents or guardians. The study was conducted in Hospital Jose Domingo de Obaldia, David, Republic of Panama (67 patients) and at the Whiteriver Public Health Service Indian Hospital, Whiteriver, Arizona (17 patients) and

the Arizona Health Sciences Center, Tucson, Arizona (1 patient), between August 1985 and April 1987.

The protocol was approved by the committees on human volunteers in all the participating institutions.

Treatment groups

Upon enrollment into the study, and following a standardized history and physical examination, the patients were randomized to one of the three treatment groups, using a block random number table in groups of six. Each treatment group was given one of three oral rehydration solutions, whose composition is shown in Table 1. Group A received a solution containing hydrolyzed lactalbumin plus carbohydrates and electrolytes (LAD-ORS); group B received an identical solution, but without the hydrolyzed lactalbumin (MS-ORS) and group C received a standard glucose–electrolyte solution (G-ORS). The sodium content (60 mmol/l) and the other electrolyte components were identical in the three solutions. The hydrolyzed lactalbumin is composed of approximately 70% free amino acids and small peptides (di-, tri- and tetrapeptides) and about 30% of longer peptides. Its amino acid composition is given in Table 2.

All three solutions were prepared and supplied by Nestle (Vevey, Switzerland) in 250-ml wax cartons, lined with aluminium foil. All identifying labels on the cartons were replaced with a coded five digit number. Only the pharmacists dispensing the solutions knew the identify of the code. The solutions were all clear; the LAD-ORS had a slight yellowish hue that could only be detected against a white background.

Therapy

Rehydration phase. All patients who were assessed as severely dehydrated (> 9% body weight loss) were given iv Ringer's lactose solution (40 ml/kg) until pulse and blood pressure returned to normal. Thereafter, the appropriate ORS was administered depending on the group into which the infant was randomized. Patients initially assessed as having moderate dehydration (7–9% body weight loss) were administered 80 ml/kg of the appropriate ORS and those with mild dehydration (5–6% body weight loss) were administered 60 ml/kg of the appropriate ORS. Rehydration was attempted to be completed within 4 h. At this time infants were reassessed for signs of dehydration; if dehydration persisted, the period of rehydration was continued for another 4 h.

Table 1. Oral rehydration solutions used in study.

	Solution A (LAD-ORS)	Solution B (MS-ORS)	Solution C (G-ORS)
Sodium (mmol/l)	60	60	60
Potassium (mmol/l)	20	20	20
Chloride (mmol/l)	50	50	50
Citrate (mmol/l)	30	30	30
Maltodextrin (g/l)	60	60	—
Sucrose (g/l)	20	20	—
Hydrolyzed lactalbumin (LAD) (g/l)	4	—	—
Dextrose (g/l)	—	—	20
Osmolarity (mosm/l)	302	298	260
Energy (kcal/l)	336	320	80

Table 2. Amino acid composition of hydrolyzed lactalbumin used in LAD-ORS[a].

Amino acid	Percent of total free amino acids
Histidine	2.4
Isoleucine	6.8
Leucine	10.1
Lysine	10.0
Methionine	2.1
Cystine	1.8
Phenylalanine	3.4
Tyrosine	3.1
Threonine	8.3
Tryptophan	1.9
Valine	6.3
Arginine	2.9
Alanine	5.4
Aspartic acid	10.9
Glutamic acid	18.9
Glycine	2.1
Proline	6.8
Serine	5.6

[a] Composition is similar to cow's milk whey protein.

Maintenance. After rehydration was completed, infants in each group continued to receive only the appropriate ORS for the next 24 h at a rate of 150 ml/kg. At the end of this 24-h period of maintenance therapy, a soy-based formula (Nursoy, Wyeth Laboratories) was then given at a rate of 150 ml/kg/24 h until discharge from hospital. Ongoing stool losses were replaced on a 1:1 basis with the appropriate ORS throughout the remainder of the hospitalization. The study protocol treatment was terminated when the diarrhoea had resolved, defined as the time of the last liquid stool, followed by a continuous 16-h period without diarrhoea.

Intake and output measurements. Intake of all iv and oral fluids was measured and recorded until the diarrhoea resolved. 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. Naked body weights were taken at admission, 4, 8 and 28 h after admission, and every 24 h thereafter until discharge.

Antibiotic therapy. The use of antibiotics was permitted to treat suspected or culture-proven *Shigella* infections and any concurrent illness, such as otitis media or pneumonia. Antibiotic therapy was stopped if appropriate cultures were negative.

Laboratory studies. Upon admission, blood specimens were obtained from each patient for measurement of electrolytes, blood urea nitrogen, glucose, haematocrit and total protein. Stool specimens were obtained for identification of *Salmonella* and *Shigella* using standard techniques (17) in both the United States and Panama; other bacterial enteropathogens were not routinely sought. Rotavirus, however, was routinely assayed by saving an aliquot of stool in 10% phosphate-buffered saline solution, which was frozen for later identification of antigen by enzyme-linked immunosorbent assay (18) in the laboratory of Dr Robert Yolken.

At 8 and 24 h after admission and at discharge, additional blood specimens were obtained to repeat the initial studies performed on admission.

Treatment failures

Patients were considered to be treatment failures and removed from the study if any of the following occurred: (1) serum electrolyte values (in mmol/l) were abnormal at specific time intervals, i.e. potassium < 2.5 or > 6 and bicarbonate < 10 at 8 h or later after admission and sodium < 125 or > 150 at 24 h or later after admission; (2) if the stool output exceeded 10 ml/kg/h in any 8-h period after the first 16-h period and/or the patient was unable to drink adequate amounts of fluids to maintain hydration; (3) if severe vomiting prevented adequate rehydration with ORS; and (4) the diarrhoeal illness continued for more than seven days. Children considered failures were treated individually by the patients' primary physicians according to medical indications.

Statistical methods

The data were analysed using CLINFO computer software and all initial comparisons made by ANOVA. 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 distribution and equal variances, and modified appropriately for unequal variances. The Wilcoxon non-parametric test was used when the distribution was not normal.

Sample size was calculated to ensure the detection of a 50% difference in either total stool output or duration of diarrhoea, with a power of 80% and an alpha error of 0.05. A total of approximately 30 patients per group was required, based on data from previous studies in the United States and Panama (1, 9).

Results

A total of 85 children (67 in Panama and 18 in Arizona) were enrolled into the study. There were 7 failures (described in detail later) and 4 children in whom there was a break in protocol (necessitating the omission of their complete data), thus leaving a total of 74 patients who successfully completed the study.

Admission characteristics

The admission characteristics of all 85 patients are shown in Table 3. No differences were found among the different parameters measured between the groups.

About one-fifth of the children had fever and one-third had vomiting on admission. Approximately 20% had received antibiotics. The illness, on average, was of about 2–3 days' duration. Rotavirus was clearly the major pathogen, occurring in 36 of 67 (54%) children; group C (S-ORS) had the highest percentage of rotavirus isolations (80%) which was significantly greater than group A (LAD-ORS) only ($p = 0.005$).

Success of treatment

The overall success rate was 91.4% (74/81) when those patients who had to be dropped because of a break in protocol were excluded. These data (Table 4) showed no significant differences in success rates between treatment groups. The reasons for the 8 failures were: 2 patients had persistent vomiting; 1 patient each had persistent hyponatraemia, persistent hypokalaemia, hypernatraemia, fever, seizure of unknown aetiology and high stool output.

The use of antibiotics during hospitalization was similar in the three groups.

Output variables

These are summarized in Table 4. There were no significant differences in duration of diarrhoea, stool output, urine output or volume of vomitus.

Intake variables

The intake of oral rehydration solutions was similar in all three groups, as was the intake of soy formula (Table 4).

Serum electrolytes

Mean sodium values were within normal limits at the time of admission and throughout therapy in all groups (see Table 3). On admission, there were, however, 2 patients with hyponatraemia and 7 with hypernatraemia. Six of the latter were among the 18 studied

Table 3. Admission characteristics of treatment groups. Values are mean ± SD or number (%).

	n[a]	Group A (LAD-ORS)	n	Group B (MS-ORS)	n	Group C (S-ORS)
Age (months)	29	8.9 ± 3.5	28	8.1 ± 2.9	28	8.9 ± 3.6
Sex (M/F)		15/14		17/11		16/12
Weight (kg)	26	7.5 ± 1.7	23	7.7 ± 1.1	25	8.2 ± 1.8
History of vomiting		7/21 (33%)		7/21 (33%)		8/21 (38%)
Days with diarrhoea pre-admission	29	2.9 ± 1.6	28	3.3 ± 1.9	28	2.6 ± 1.4
No. stools prior to admission	28	9.9 ± 4.6	28	9.1 ± 4.4	27	9.3 ± 3.4
Prior antibiotics		3/26 (11.5%)		6/22 (27%)		7/21 (33%)
History of fever		5/24 (20.8%)		3/25 (12%)		6/21 (28%)
Temperature	29	38.2 ± 0.6	27	38.2 ± 0.9	27	38.5 ± 0.9
Serum sodium	28	140 ± 7	27	137 ± 10	27	140 ± 9
Serum potassium	28	4.0 ± 0.9	28	3.7 ± 0.9	28	3.9 ± 0.8
Serum chloride	28	103 ± 8	26	105 ± 8	28	105 ± 11
Serum bicarbonate	28	15.1 ± 4.8	28	14.5 ± 4.1	28	14.9 ± 4.5
Total protein	19	7.0 ± 0.9	26	7.1 ± 0.9	20	7.1 ± 0.8
Blood urea nitrogen	28	13.0 ± 7.5	28	13.1 ± 6.6	26	12.5 ± 5.7
Glucose	28	110 ± 66	26	89 ± 21	26	91 ± 23
Haematocrit	17	34 ± 5	21	35 ± 4	16	36 ± 5
Dehydration						
Mild		17		19		21
Moderate		11		9		7
Severe		1		0		0
Aetiological agents						
Rotavirus		8/24 (33%)		12/23 (52%)		16/20 (80%)**
Shigella		2		3		0
Salmonella		1		0		0

[a] n given when less than total.
** $p = 0.005$ compared to group A; other groups not significantly different.

in Arizona. One of the Panamanian children with hyponatraemia on admission (113 mmol/l) continued to be hyponatraemic at 24 h (115 mmol/l) and was removed from the study as a failure.

At 8 h there were 11 children with abnormal sodium values; at 24 h only 3. At discharge only 1 child had an abnormal sodium value (152 mmol/l). The abnormal values were equally distributed among the three treatment groups (data not shown) and none was associated with clinical symptoms.

There were 2 children with hypokalaemia on admission (both 2.3 mmol/l) and 1 with hyperkalaemia (5.5 mmol/l). These values all returned to normal during therapy. There were small but statistically significant differences in potassium and chloride values at 24 h only (see Table 4). All three groups' mean values, however, were within the normal range.

There were no significant abnormalities in other parameters measured during therapy, such as blood urea nitrogen, glucose and total protein (data not shown).

Weight gain during therapy

The average weight gain from admission to discharge from the study was between 3.9 and 6.5% (Table 4). The children ingesting the LAD-ORS had the greatest weight gain at 28 h and at resolution, while the group receiving S-ORS had the least weight gain at this time. The differences between the LAD-ORS and S-ORS groups were statistically significant. The group receiving MS-ORS was intermediate in weight gain and not significantly different from the S-ORS group. Only at the time of resolution was the weight gain of the LAD-ORS group significantly greater than that of the MS-ORS group. At the two-week follow-up, however, there were no significant differences between the three groups, when compared to discharge weight.

Discussion

This study demonstrates that all three oral rehydration solutions had similar efficacy and there were no significant differences among them in treatment outcome. Specifically, there were no differences in stool output or length of diarrhoeal illness, which would have indicated improved intestinal absorption of sodium and water.

These findings are similar to those reported recently in which the addition of glycine (9, 19, 20) or of glycine and glycyl-glycine to either a glucose-based ORS (21, 22) or a maltodextrin-based ORS failed to show an improvement in either stool output or duration of

Table 4. Measurements of treatment during diarrhoea. Values are mean ± SD or number (%).

	n	Group A (LAD-ORS)	*n*	Group B (MS-ORS)	*n*	Group C (S-ORS)
Total patients admitted		29		28		28
No. dropped due to break in protocol		1		1		2
Failures/Total		3/28 (10.7%)		4/27 (14.8%)		1/26 (3.8%)
Antibiotics during hospitalization		9/26 (35%)		7/28 (25%)		10/26 (38%)
Stool output (ml/kg)						
0–4 h	25	10.9 ± 8.6	23	12.7 ± 9.2	25	12.8 ± 14.3
5–28 h	25	63 ± 39	23	65 ± 38	25	64 ± 40
Total during illness	25	151 ± 95	23	153 ± 74	25	137 ± 84
Total vomitus output (ml/kg)	18	19 ± 19	15	33 ± 34	17	20 ± 19
Total urine output (males)	11	139 ± 47	13	114 ± 81	14	117 ± 65
ORS intake (ml/kg)						
0–4 h	25	46.2 ± 18.8	23	47.9 ± 13.6	25	40.9 ± 22.4
5–28 h	25	172 ± 66	23	184 ± 71	25	167 ± 54
Total during illness	25	284 ± 99	23	304 ± 92	25	259 ± 92
Soy formula intake (ml/kg)						
Total during illness	25	128 ± 74	23	147 ± 82	25	140 ± 99
Duration of illness (h)	25	47.7 ± 20.3	23	55.4 ± 25.1	25	56.8 ± 28.2
Serum sodium (mmol/l)						
8 h	22	139 ± 7	22	138 ± 11	24	139 ± 8
24 h	22	139 ± 7	22	141 ± 11	24	140 ± 5
Discharge	22	137 ± 6	22	140 ± 5	24	137 ± 4
Serum potassium (mmol/l)						
8 h	25	3.9 ± 0.9	23	3.9 ± 0.6	25	4.4 ± 1.0
24 h	25	3.8 ± 0.7	23	3.7 ± 0.7	25	4.4 ± 0.6*
Discharge	25	4.4 ± 0.7	22	4.3 ± 0.5	25	4.3 ± 0.4
Percent weight gain						
4 h	26	1.4 ± 2.5	23	1.4 ± 3.4	25	0.7 ± 2.4
28 h	24	4.8 ± 3.5	23	3.1 ± 2.9	25	2.2 + 3.2+
At resolution++	25	6.5 ± 3.4	23	4.5 ± 2.6	25	3.9 ± 5.6
At 2 weeks compared to discharge weight	20	3.8 ± 5.0	16	4.0 ± 2.7	18	4.8 ± 5.9

* $p = 0.002$, compared to A and B. + Group C versus A, $p < 0.01$; ++ Group C versus A, $p = 0.005$; group B versus A, $p = 0.03$.

diarrhoea, when compared to standard glucose-based ORS.

In this study, the only differences in outcome variables were in weight gain. The children receiving the S-ORS solution, which had the lowest number of calories, gained the least amount of weight. However, this difference could not be explained solely on the caloric content of the ORS since (1) the difference in caloric intake would not be adequate to explain the weight differences and (2) only one of the two ORS solutions with the greater amount of calories (LAD-ORS) demonstrated a significant difference. It would seem that these differences may be explained by slight differences in severity of dehydration at the time of admission (as estimated by clinical examination), although these parameters were not significantly different. At the two-week follow-up, weight gain, as compared to the time of discharge, was similar among the three groups.

The most common aetiological agent at both locations was rotavirus; 54% of all study children had this agent detected in stool. The isolation rate was significantly higher in the S-ORS group, which may have suggested that this group would present with more severe disease; this, however, was clearly not the case. Identification of enteropathogens other than rotavirus was limited; diarrhoeagenic *Escherichia coli* were not sought and *Campylobacter* isolation was possible only at the Arizona site. *Salmonella* and *Shigella*, however, were infrequent aetiological agents, as would be expected from other similar type studies (1, 9).

The original hypothesis, that the addition of defined substrates (amino acids, di- and tripeptides) which use different intestinal transport mechanisms in an oral rehydration solution might significantly enhance sodium chloride and water absorption was not substantiated in this study. On the other hand, the use of less defined substrates, such as rice, has resulted in significant decreases in stool output according to many published studies (10–12). Whether or not these differences are due to the substrates involved, or to their concentrations, is not completely known. Recent

studies in animals (23) and humans (24) have suggested that a hypotonic ORS solution may be absorbed significantly better than isotonic solutions. Both the LAD-ORS and the MS-ORS had higher osmolalities (approximately 40 mosm/l) than G-ORS, which could have masked a possible reduction in stool volume.

A soy-based formula was used during the study to standardize fluid and caloric intake, and to avoid potential problems of lactose malabsorption. We do not mean to imply that this formula is necessary for treating diarrhoea adequately outside of a study situation.

The overall failure rate of ORS (7/71) of 10% in this study is comparable to studies elsewhere (1, 9, 25). Likewise, the lack of significant electrolyte abnormalities occurring during therapy are comparable to other similar studies (1, 9, 25).

In summary, the LAD-ORS failed to effect any decrease in stool output over the control groups. All three test solutions were in effect identical in treatment outcome measurements, with the one exception being the temporarily increased weight gain seen in children receiving the LAD-ORS which could not be readily explained.

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