

ORAL REHYDRATION THERAPY OF INFANTILE DIARRHEA

A Controlled Study of Well-Nourished Children Hospitalized in the United States and Panama

MATHURAM SANTOSHAM, M.D., ROBERT S. DAUM, M.D., LUDWIG DILLMAN, M.D.,

JOSE L. RODRIGUEZ, M.D., SARAH LUQUE, M.D., REBECCA RUSSELL, M.D.,

MIGUEL KOURANY, PH.D., ROBERT W. RYDER, M.D., ALFRED V. BARTLETT, M.D.,

ALLAN ROSENBERG, M.D., ABRAHAM S. BENENSON, M.D., AND R. BRADLEY SACK, M.D., Sc.D.

Abstract Although oral glucose-electrolyte solutions containing 90 mmol of sodium per liter have been widely used in the treatment of acute diarrhea among undernourished children in the developing world, they have rarely been studied in well-nourished children. We therefore conducted a controlled, randomized study among well-nourished children three months to two years old who were hospitalized with acute diarrhea (52 in the United States, and 94 in Panama), to compare the efficacy of this solution with that of one containing 50 mmol of sodium per liter and with standard intravenous therapy.

ORAL glucose-electrolyte solutions have been shown during the past 10 years to be highly effective in the treatment of dehydration secondary to acute diarrhea in the developing world.¹⁻³ This therapy is based on the simple physiologic observation that active glucose absorption in the small bowel promotes the absorption of sodium.^{4,5} Oral rehydration therapy was first developed specifically for the treatment of cholera (in which intestinal glucose absorption was known to be normal), because of the need for a simpler, more available, and inexpensive treatment that could replace intravenous fluids, which were often unavailable in cholera-endemic areas.⁶⁻¹¹ Since these early studies, oral rehydration therapy has been widely used to treat other types of acute diarrhea, including those caused by enterotoxigenic *Escherichia coli*^{9,11-13} and rotavirus.¹⁴ Furthermore, oral rehydration therapy employing a single formula with a sodium concentration of 90 mmol per liter^{2,3} has been used successfully in patients of all ages, including newborns¹⁵ in countries of the developing world and in American Indian populations.¹³ The success of this simple form of treatment has been remarkable, and it now forms the backbone of the diarrheal-disease control program of the World Health Organization (WHO), a global effort to reduce mortality and morbidity from diarrheal diseases.^{2,16} In such an effort there is obviously a need for a universal solution that can be given by untrained personnel to all patients with diarrhea.

In the United States, oral therapy for diarrhea was used earlier on an empirical basis¹⁷; at present there are pharmaceutical preparations on the market for use

in mild diarrhea.¹⁸ It was not previously appreciated, however, that oral rehydration therapy could correct both initial water and electrolyte deficits in patients with mild to moderate dehydration, as well as compensate for losses due to continuing diarrhea. Furthermore, hypernatremia had been reported to occur with early oral rehydration solutions containing 50 mmol of sodium per liter and 8 per cent glucose¹⁸; at that time the hypernatremia was thought to be secondary to the sodium concentration of the solution rather than to the high carbohydrate load, which now seems the more likely cause.¹ Thus, there has been considerable reluctance to adopt oral rehydration therapy in the "developed" countries, except for mild diarrhea in patients who are not clinically dehydrated. The reasons usually given in the United States for avoiding use of the oral rehydration formula of the WHO include the following observations: fecal sodium concentration is generally less than 90 mmol per liter in patients with infantile diarrhea not due to cholera, and thus there has been concern about the possible development of hypernatremia, particularly in well-nourished children¹⁸⁻²⁰; the vomiting that frequently accompanies gastroenteritis is thought to contraindicate oral rehydration therapy; and intravenous therapy is readily available in the United States. Unfortunately, the reluctance of pediatricians in developed countries to accept oral rehydration therapy as standard practice has been reflected in the recommendations given by textbooks of pediatrics, which are often recognized as authoritative by physicians in the developing world.

We conclude that glucose-electrolyte oral solutions containing either 50 or 90 mmol of sodium per liter are effective and safe in the treatment of well-nourished children hospitalized with acute diarrhea, and that they may completely replace intravenous fluids in the majority of such children. (N Engl J Med. 1982; 306:1070-6.)

In an attempt to resolve these issues, we undertook a controlled trial of oral rehydration therapy in well-nourished American children admitted to United States hospitals who had dehydration secondary to acute diarrhea. Two oral solutions, differing only in sodium chloride content (90 mmol and 50 mmol of sodium per liter), were compared with intravenous regimens employed as standard practice in United States hospitals. Because of the low number of admissions for diarrhea in most United States hospitals, the study was expanded to Panama City, Panama,

From the Division of Geographic Medicine, the departments of Medicine, Baltimore City Hospitals and the Johns Hopkins University School of Medicine, Baltimore, Md.; Social Security Hospital and Gorgas Memorial Laboratory, Panama City, Panama; and the Department of Pediatrics, Tulane University School of Medicine, New Orleans. Address reprint requests to Dr. Santosham at the Baltimore City Hospitals, Division of Geographic Medicine, 4940 Eastern Ave., Baltimore, MD 21224.

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where the same protocol was used in well-nourished children.

METHODS

Patients

The study population consisted of 146 well-nourished children of both sexes whose length and weight for age were above the third percentile (according to standards published by the United States National Center for Health Statistics, 1976²¹) and who were three months to two years old. They had been hospitalized with the diagnosis of dehydration secondary to acute diarrhea of less than five days' duration. Fifty-two of the children were studied over a four-year period (July 1977 to March 1981) in four hospitals in the United States (Charity Hospital, New Orleans, 27 patients; Baltimore City Hospitals, Baltimore, 21 patients; St. Agnes Hospital, Baltimore, three patients; and the University of Maryland Hospital, Baltimore, one patient). The other 94 children were hospitalized at the Social Security Hospital in Panama City during a five-month period (December 1979 to March 1981). The same protocol was used in all hospitals, with the few exceptions listed below. Prior approval of the study protocol was obtained by the appropriate institutional committees on volunteers.

All patients were initially examined by the house officers in the hospital (independently of the investigators), and the decision to hospitalize was based on their clinical assessment that dehydration of 5 per cent or more was present. At admission, informed consent was obtained from the parents or guardians, and the children were randomized to one of three treatment groups (A, B, or C). Patients were admitted to the study regardless of their state of nutrition; however, only those determined to be well nourished (94 of 102 in Panama, and all 52 children in the United States) were considered in the analysis presented below.

Laboratory Studies

Laboratory studies performed on admission included blood sampling for serum levels of sodium, potassium, chloride, and bicarbonate, for blood urea nitrogen, for hematocrit, and for total serum solids; stool sampling (rectal catheter) for electrolyte content (performed in Panamanian children only); parasitologic examination²²; detection of the rotavirus antigen by the enzyme-linked immunosorbent assay²³ (at all hospitals except Tulane University, where electron microscopy was used²⁴); and bacteriologic examination for enteric pathogens, including enterotoxigenic *Esch. coli*.²² Follow-up laboratory studies were performed eight, 24, and 48 hours after admission (serum sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and total serum solids). Convalescent blood samples for determining electrolyte levels were obtained in the Panamanian children two weeks after discharge.

In the United States the study protocol was followed by the house officers in each hospital, under our supervision. In Panama the study was conducted under the direct supervision of two of us (M.S. and L.D.).

Treatment Groups

Patients in Group A received Solution A, the standard WHO glucose-electrolyte formula containing 90 mmol of sodium per liter, with a strawberry flavoring; patients in Group B received Solution B, which was identical to Solution A except that the sodium chloride content was reduced to produce a sodium concentration of 50 mmol per liter (Table 1) and the flavoring was omitted. Patients in Group C (the control group) received what was considered standard therapy in the hospitals in the study²⁵; they were given 0.45 per cent intravenous saline with 5 per cent glucose and 20 mmol of potassium chloride per liter for rehydration and maintenance, which was followed by oral Pedialyte (Ross Laboratories, Columbus, Ohio) (Table 1) as described below. Nurses prepared Solutions A and B by mixing the appropriate prepackaged ingredients (provided by Pennwalt Laboratories) to a total volume of 1 liter with tap water.

Irrespective of assigned treatment groups, patients who were considered to be severely dehydrated on admission (estimated dehydra-

Table 1. Composition of Solutions Used for Oral Therapy of Acute Diarrhea.

INGREDIENT	CONCENTRATION		
	SOLUTION A*	SOLUTION B†	PEDIALYTE‡
	mmol/liter		
Sodium	90	50	30
Potassium	20	20	20
Chloride	80	40	30
Bicarbonate	30	30	—
Glucose	111	111	277
Citrate	—	—	31
Osmolarity (mOsm/liter)	333	251	388

*Made by adding the following to 1 liter of water: sodium chloride, 3.5 g; sodium bicarbonate, 2.5 g; potassium chloride, 1.5 g; and glucose, 20 g.

†Made by adding the following to 1 liter of water: sodium chloride, 1.7 g; sodium bicarbonate, 2.5 g; potassium chloride, 1.5 g; and glucose, 20 g.

‡Also contains magnesium (2 mmol per liter) and calcium (1 mmol per liter).

tion of approximately 10 per cent, signs of shock, or both) were given Ringer's lactate (20 ml per kilogram of body weight per hour) until the blood pressure and pulse returned to normal. Subsequently, those assigned to Group A or B completed rehydration and maintenance therapy with the respective oral solutions. Those assigned to Group C continued to receive intravenous rehydration therapy as previously described for this group. Patients who were mildly to moderately dehydrated (estimated at 5 to 8 per cent) on admission were both initially rehydrated and maintained only with Solution A or B or with intravenous fluids (Group C). In all groups the initial calculated deficit was replaced over the first eight hours on the basis of the clinical assessment of dehydration on admission. Oral solutions were administered in a supervised ad libitum fashion. Stool losses were replaced on a 1:1 approximation with either oral or intravenous fluids, according to treatment group.

In the United States hospitals no additional free water was given to any group for the first 24 hours unless the diarrhea stopped within 24 hours. After the diarrhea stopped, patients in Groups A and B were given Isomil (a soy-based lactose-free formula [Ross Laboratories] diluted 1:1 with water. A regular diet was resumed within the next 24 hours. Patients in Group C were first given Pedialyte (Table 1) for 12 hours after the diarrhea stopped and then diluted (1:1) Isomil and the regular diet as in Groups A and B.

In the Panamanian hospitals the protocol was identical except that eight hours after admission, foods (rice cereal with water, as well as bananas and applesauce mixed with water in purced form) were allowed in addition to the treatment solutions, whether or not the diarrhea continued, because this was the standard hospital practice.

Each patient's weight and the volume of fluid administered were recorded every four hours. Stools and vomitus were measured every four hours by determining the difference in weight between dry and wet or soiled diapers and linen. Urine output was measured separately from stool output; in the boys urine bags were used, and in the girls urine was often mixed with stools and measured along with them (weight difference between wet and dry diapers). Physical examination was also repeated eight hours after admission to assess the state of hydration.

Diarrhea was considered to be present if the stools took the shape of their container; it was considered to have stopped when the last diarrheal stool was passed. The treatment of patients receiving oral rehydration solutions was defined as a failure if the patients would not take oral fluids, if marked signs of initial dehydration persisted beyond eight hours, or if evidence of dehydration returned during maintenance therapy.

The two-tailed t-test was used to analyze differences of means between the groups.

RESULTS

All but one of the 146 children were successfully treated according to the protocol of the treatment

group into which they were randomized. One child in Group A in the United States (described below) required additional unscheduled intravenous fluids, and therefore treatment was considered to have failed in this patient. All patients who had abnormal sodium or potassium levels on admission (Fig. 1) were successfully treated, with return of electrolyte levels to normal; furthermore, neither hypernatremia nor hyponatremia developed during therapy in any patient.

Clinical Comparison on Admission (Table 2)

At admission there were no significant differences in clinical characteristics within the population groups in the United States or Panama. An etiologic agent was identified in 54 of the Panamanian children (57 per cent) and in 11 of the United States children (21 per cent). There were no differences between the treatment groups. Only three children (those with confirmed shigella infections) were treated with antibiotics. Hydration was completed by the time antibiotics were given.

Clinical Course of Illness (Tables 3 and 4)

Comparisons of intake, output, duration of diarrhea, and percentage of weight gain were made between the three treatment groups in the two countries. Eleven children in Groups A and B received intravenous fluids on admission (mean length of administration, 4.8 ± 1.2 hours [S.E.]) because they were judged to be severely dehydrated. In both the United States and Panama, children in Group A took in significantly

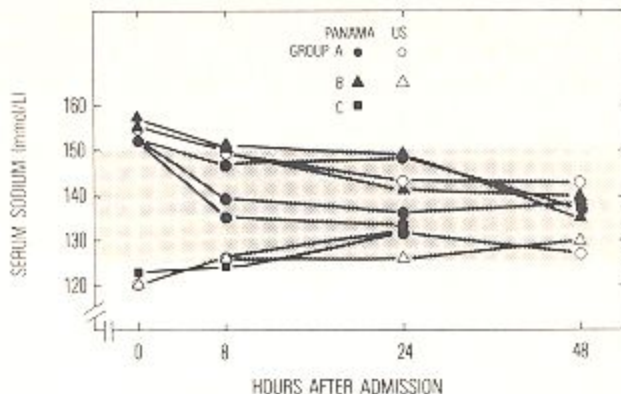


Figure 1. Serum Sodium Concentrations during Therapy in Patients Who Had Abnormal Values on Admission, Plotted According to Treatment Group.

Each symbol denotes one patient. Groups A and B received oral fluid containing 90 mmol of sodium per liter and 50 mmol per liter, respectively; Group C received primarily intravenous fluids (see text for details). Only one patient in the oral therapy groups (Group B, U.S. [hyponatremia]) received initial intravenous therapy.

The shaded area represents an expanded normal range that is considered clinically safe.

more sodium than children in Group B (about 50 to 75 per cent more) both during the first eight hours and for the entire hospitalization. Furthermore, in both oral-therapy groups the United States children took in more sodium than the Panamanian children ($P < 0.01$), which perhaps reflects the eagerness of the staffs in the United States hospitals to have the chil-

Table 2. Features of the Treatment Groups on Admission.

FEATURE	PATIENTS IN THE UNITED STATES *			PATIENTS IN PANAMA *		
	GROUP A	GROUP B	GROUP C	GROUP A	GROUP B	GROUP C
Total in group	20	15	17	30	33	31
Age (mo)	11±2	10±2	9±1	10±1	11±1	10±1
Male:Female	12:8	9:6	7:10	16:14	17:16	20:11
Body weight at discharge (kg)	8.5±0.6	8.4±0.6	8.2±0.5	8.1±0.3	9.0±0.5	8.7±0.4
No. with history of vomiting	14 (70)	12 (80)	11 (65)	27 (90)	28 (85)	28 (90)
Days of diarrhea before admission	2.6±0.3	3.5±0.6	2.6±0.4	3.7±0.4	3.0±0.3	3.2±0.4
Temperature (°C)	37.6±0.3	37.3±0.2	37.9±0.3	37.8±0.9	37.9±1.2	38.1±1.1
No. given antibiotics before admission	0	1 (7)	1 (6)	10 (30)	12 (36)	11 (35)
Serum sodium (mmol per liter)	138±2	139±2	139±2	138±1	137±1	135±1
Serum potassium (mmol per liter)	4.4±0.1	4.2±0.2	4.3±0.2	3.9±0.1	4.0±0.1	3.7±0.1
Serum bicarbonate (mmol per liter)	14±1	15±1	14±1	12±1	13±1	15±1
Hematocrit	35±1	36±1	38±1	34±1	37±1	36±1
Total serum solids (g/dl)	7.0±0.3	6.4±0.2	6.8±0.2	7.1±0.1	7.2±0.1	7.1±0.2
Blood glucose (mg/dl) †	93±8	125±18	97±6	128±22	111±7	107±8
Blood urea nitrogen (mg/dl) ‡	23±3	25±6	24±3	19±2	14±1	20±2
Stool sodium (mmol per liter) §	—	—	—	42±7	45±6	49±8
Stool potassium (mmol per liter) §	—	—	—	30±5	36±6	37±5
Estimated degree of hydration						
Mild (5-6%)	16 (80)	10 (67)	9 (53)	17 (57)	23 (70)	14 (45)
Moderate (7-8%)	3 (15)	3 (20)	7 (41)	9 (30)	7 (21)	14 (45)
Severe (>8%)	1 (5)	2 (13)	1 (6)	4 (13)	3 (9)	3 (10)
Pathogens identified in stools						
Rotavirus	2	4	2	16	16	15
Salmonella	2	1	0	1	0	1
Shigella	0	0	0	1	1	1
Enterotoxigenic <i>Esch. coli</i>	0	0	0	0	1 ¶	1

*Values denote means ± S.E. Figures in parentheses denote percentages. None of the differences between the groups were significant.

†To convert to millimoles per liter, multiply by 0.055.

‡To convert to millimoles per liter, multiply by 0.36.

§Determined only in Panamanian patients (20 in Group A, 22 in Group B, and 19 in Group C).

¶Produced heat-labile toxin.

||Produced both heat-labile and heat-stable toxin.

dren drink large amounts of fluid. In spite of this, the children in the United States gained significantly less weight — a finding that is consistent with the fact that they were less dehydrated on admission but excreted more urine (e.g., urine excreted by boys in Groups A and B [10 United States patients vs. 15 Panamanian patients] during the period of diarrhea, 80 ± 18 vs. 19 ± 5 ml per kilogram; $P < 0.05$).

Serum Electrolytes

On admission six patients were hypernatremic (serum sodium > 150 mmol per liter) and three were hyponatremic (serum sodium < 125 mmol per liter) (Fig. 1). In addition, three United States children (one in Group B and two in Group C) were hyperkalemic on admission (serum potassium > 5.5 mmol per liter); one Panamanian child (Group B) was hyperkalemic, and two children (Groups A and C) were hypokalemic (serum potassium < 2.5 mmol per liter). All did well with therapy, and their serum levels returned to normal.

The mean serum electrolyte levels in the three treatment groups were normal (data not shown) at eight, 24, and 48 hours. However, two Panamanian patients in Group C were normokalemic on admission but became hypokalemic 24 hours after admission (serum potassium < 2.4 mmol per liter in both). These levels returned to normal and were not associated with symptoms.

Table 3. Features of the Treatment Groups during Therapy — United States Study.

FEATURE	TREATMENT GROUP *		
	A (n = 20)	B (n = 15)	C (n = 17)
No. of patients receiving intravenous fluids (per cent)	1 (5)	3 (20)	17 (100)
Intake of treatment solution during first 8 hr (ml/kg)	93 ± 12	80 ± 12	55 ± 6 †
Intake of sodium during first 8 hr (mmol/kg)	8.3 ± 1.1	4.0 ± 0.6 ‡	3.2 ± 0.7 ‡
Total intake of treatment solution during illness (ml/kg)	271 ± 40	271 ± 36 §	163 ± 18 ¶; 68 ± 12
Total intake of sodium during illness (mmol/kg)	27.9 ± 4.8	13.6 ± 1.8 ‡	9.7 ± 1.0 ‡
Intake other than treatment solution (ml/kg) **	107 ± 36	130 ± 31	171 ± 35
Stool output during first 8 hr (mg/kg/hr)	4.6 ± 0.9	4.2 ± 1.0	2.3 ± 0.5
Total stool output during illness (ml/kg)	181 ± 33	193 ± 25 ††	112 ± 13 †
Duration of diarrhea after hospitalization (hr)	33 ± 5	33 ± 6	34 ± 5
Per cent weight gain at discharge	4.3 ± 0.8	2.8 ± 0.7	5.0 ± 0.1

*Values denote means \pm S.E.

†Significantly different from value for Group A ($P < 0.02$).

‡Significantly different from value for Group A ($P < 0.01$).

§Significantly different from values for Group C ($P < 0.01$).

¶Value for all intravenous fluids.

||Value for Pedialyte.

**Similac, Isomil, and water.

††Significantly different from value for Group C ($P < 0.02$).

Follow-up Studies at Two Weeks

Serum electrolyte levels were normal in all 41 Panamanian patients examined (17 in Group A, 12 in Group B, and 12 in Group C).

Treatment Failure

Oral rehydration therapy was considered to have failed in one patient (United States population, Group A). This patient, admitted with clinically severe hyponatremic dehydration, was treated according to protocol and did well while receiving oral therapy for the first 20 hours. At the time the stool output had increased to 11 ml per kilogram per hour during the eight-hour period and signs of dehydration had returned; intravenous therapy was therefore reinstated. The child did well, and the diarrhea stopped 24 hours after admission. Testing of stools for reducing substances was negative throughout the hospitalization. No etiologic agent was identified in this patient's stools.

Complications

In Group A periorbital edema developed after 48 hours of oral therapy in two United States children who were mildly dehydrated on admission. Both had received Solution A in considerable excess of their diarrheal output. The first patient had a total stool output of 187 ml per kilogram, and diarrhea stopped 16 hours after admission; however, the patient had re-

Table 4. Features of the Treatment Groups during Therapy — Panamanian Study.

FEATURE	TREATMENT GROUP *		
	A (n = 30)	B (n = 33)	C (n = 31)
No. of patients receiving intravenous fluids (per cent)	4 (13)	3 (9)	31 (100)
Intake of treatment solution during first 8 hr (ml/kg)	59 ± 5 †	58 ± 7	86 ± 5 ‡
Intake of sodium during first 8 hr (mmol/kg)	5.5 ± 0.5	3.2 ± 0.5 §	5.9 ± 0.4 ¶
Total intake of treatment solution during illness (ml/kg)	89 ± 8	105 ± 10	192 ± 13 ‡
Total intake of sodium during illness (mmol/kg)	8.5 ± 0.8 **	5.9 ± 0.7	6.3 ± 1.0
Intake other than treatment solution (ml/kg) ††	103 ± 12	82 ± 10	90 ± 14
Stool output during first 8 hr (ml/kg/hr)	4.3 ± 0.6	4.3 ± 0.8	4.8 ± 0.5
Total stool output during illness (ml/kg)	90 ± 10 §	113 ± 20	168 ± 9 **
Duration of diarrhea after hospitalization (hr)	34 ± 2	34 ± 2	34 ± 2
Per cent weight gain after hydration	6.7 ± 0.5	6.3 ± 0.3	6.7 ± 0.5

*Values denote means \pm S.E.

†Significantly different from value for Group C ($P = 0.01$).

‡Significantly different from value for Group B ($P = 0.001$).

§Significantly different from value for Group C ($P < 0.001$).

¶Significantly different from value for Group B ($P < 0.001$).

||Significantly different from value for Group C ($P = 0.001$).

**Significantly different from value for Group B ($P < 0.05$).

††Similac, Isomil, bananas, rice cereal, applesauce, and water.

ceived 342 ml of solution per kilogram over a 48-hour period. The second patient had a total stool output of 212 ml per kilogram, and diarrhea stopped after 48 hours; this patient received 475 ml of the oral solution per kilogram during this period. Neither child had received additional free water or food during this period, and both remained asymptomatic and normonatremic during therapy. (The second child had been admitted with a serum sodium level of 155 mmol per liter.) The periorbital edema resolved within eight to 24 hours after discontinuation of the oral rehydration solution.

There were no complications in Group B.

There were three patients with complications in Group C. One mildly dehydrated United States patient had transient unexplained focal seizures of the left arm and mouth 16 hours after intravenous hydration was begun. The serum glucose level and electroencephalogram were normal at this time; the serum bicarbonate level was 7.4 mmol per liter, but the other electrolytes were normal. She was treated with additional glucose and bicarbonate and recovered completely, without residua. In one Panamanian patient an attempt at catheterization of the subclavian vein resulted in hydrothorax. This patient was hydrated successfully with intravenous fluids; however, he required drainage of pleural fluid and placement of a chest tube. In another Panamanian patient phlebitis developed at the intravenous site and required antibiotic therapy.

DISCUSSION

This study demonstrated that 99 per cent (97 of 98) of the children receiving oral therapy solutions were treated adequately according to the protocol of the study, and that vomiting did not prevent adequate therapy in any patient; that no serious complication developed in any child receiving either of the oral-therapy solutions; and that the vast majority (89 per cent [87 of 98]) of the well-nourished children admitted because of acute diarrhea were successfully treated entirely with oral rehydration solutions and without intravenous fluids. Although similar findings have been documented by other studies using the WHO solution (Solution A in our study) in thousands of undernourished children, this controlled study was conducted exclusively in well-nourished children in a non-Indian United States population and in a developing country.

Both solutions were effective in treating the six patients admitted with hypernatremia (four given Solution A and two given Solution B). Although Solution A has been used safely in undernourished children with hypernatremic dehydration,¹ we used it in well-nourished children with hypernatremia who were treated with oral rehydration solutions. It has been suggested that the WHO solution may aggravate hypernatremia if it is given to patients presenting with hypernatremia.¹⁸⁻²⁰ However, recent reviews of cases of hypernatremia suggest that either normal saline (154 mmol of

sodium per liter) or Ringer's lactate (130 mmol per liter) should be given for initial hydration and be followed with a fluid containing 50 to 75 mmol of sodium per liter after the initial period of hydration.^{26,27} This is approximately the same amount of sodium that is provided in the WHO solution.

Likewise, all patients with hyponatremia, hyperkalemia, or hypokalemia on admission were also successfully hydrated with both oral solutions; none had electrolyte abnormalities during therapy, and none had hypokalemia at discharge or two weeks later.

Although the United States children were considered to be less dehydrated on admission than the Panamanian children, they drank more of the oral solutions than the Panamanian children. This difference was at least partly due to the fact that feedings (unmeasured for electrolyte content) other than treatment solutions were introduced earlier in the Panamanian patients. The children in the United States did not have hypernatremia or clinical evidence of saline overload (except for the two patients with periorbital edema) even though those in Group A received three times the measured sodium load given to the Panamanian children and those in Group B received over twice the sodium load. The larger sodium loads were excreted in the urine (as measured in the boys).

As observed by other investigators, the duration of diarrhea was not longer in patients receiving oral therapy than in those receiving intravenous therapy.¹⁴ The duration of diarrhea was similar in both Panamanian and United States children in spite of the differences in feeding schedules.

The only patient who required unscheduled intravenous therapy in addition to oral therapy was in Group A and had a high stool output. Previous studies have demonstrated that therapy with the WHO formula may fail in more than 50 per cent of cases when stool output exceeds 10 ml per kilogram per hour.¹² This patient's case thus demonstrates the importance of monitoring stool output in children with diarrhea severe enough to require hospitalization.

The single complication that we observed in children receiving oral therapy was the periorbital edema in the two patients who were given excessive quantities of Solution A. This complication has been observed by others in patients given excessive volumes of the WHO solution.¹ The edema was easily reversed by discontinuing the oral solution and was not associated with hypernatremia.

Pediatricians in the United States currently recommend intravenous fluids for infants hospitalized with diarrhea, and the possible need for intravenous therapy is sometimes used to justify admitting to hospitals patients with mild diarrhea. The standards for management of hospitalized patients with diarrhea, developed jointly by the American Medical Association and the American Academy of Pediatrics, indicate that all such patients should be treated initially with intravenous therapy.²⁸ Our study clearly suggests that this is not necessary. Frequently, a history of vom-

iting is cited as an indication for intravenous therapy. Vomiting was not a limiting factor in the successful use of oral therapy in any of our patients, although over 70 per cent of them presented with a history of vomiting.

Our data support previous observations made in the developing world that oral solutions with a sodium content of 90 mmol per liter are effective and safe in well-nourished children, and thus support the concept of a single formula, as promoted by the WHO. On the other hand, our data also suggest that an oral rehydration solution containing 50 mmol of sodium is also effective and safe in areas where cholera (with its attendant high fecal excretion of sodium) is rare. The latter solution has the disadvantage of not being universally applicable, however, because its relatively low sodium content would make treating diarrhea with a high stool output (as in cholera) even more difficult.⁹

In general, oral rehydration therapy has considerable advantages over intravenous therapy for dehydration and diarrhea, even in the developed world.²⁹ The cost of the therapy is lower, much of the treatment can be given by the mother without interrupting feeding, and the discomfort of intravenous therapy is avoided.

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REFERENCES

- Hirschhorn N. The treatment of acute diarrhea in children: an historical and physiological perspective. *Am J Clin Nutr.* 1980; 33:637-63.
- Oral rehydration therapy (ORT) for childhood diarrhea. Population reports. Vol. 8. No. 6. Series L. No. 2. Baltimore, Md.: Johns Hopkins University Population Information Program, 1980.
- Sack RB, Pierce NF, Hirschhorn N. The current status of oral therapy in the treatment of acute diarrheal illness. *Am J Clin Nutr.* 1978; 31:2252-7.
- Curran PF. Na, Cl, and water transport by rat ileum *in vitro*. *J Gen Physiol.* 1960; 43:1137-48.
- Hirschhorn N, Kinzie JL, Sachar DB, et al. Decrease in net stool output in cholera during intestinal perfusion with glucose-containing solutions. *N Engl J Med.* 1968; 297:176-81.
- Nalin DR, Cash RA, Islam R, Molla M, Phillips RA. Oral maintenance therapy for cholera in adults. *Lancet.* 1968; 2:370-3.
- Pierce NF, Banwell JG, Mitra RC, et al. Oral maintenance of water-electrolyte and acid-base balance in cholera: a preliminary report. *Indian J Med Res.* 1968; 56:640-5.
- Pierce NF, Banwell JG, Mitra RC, et al. Effect of intragastric glucose-electrolyte infusion upon water and electrolyte balance in Asiatic cholera. *Gastroenterology.* 1968; 55:333-43.
- Sack RB, Cassells J, Mitra R, et al. The use of oral replacement solutions in the treatment of cholera and other severe diarrhoeal disorders. *Bull WHO.* 1970; 43:351-60.
- Nalin DR, Cash RA. Oral or nasogastric maintenance therapy in pediatric cholera patients. *J Pediatr.* 1971; 78:355-8.
- Mahalanabis D, Sack RB, Jacobs B, Mondal A, Thomas J. Use of an oral glucose-electrolyte solution in the treatment of paediatric cholera — a controlled study. *J Trop Pediatr.* 1974; 20:82-7.
- Sack DA, Islam S, Brown KH, et al. Oral therapy in children with cholera: a comparison of sucrose and glucose electrolyte solutions. *J Pediatr.* 1980; 96:20-5.
- Hirschhorn N, Cash RA, Woodward WE, Spivey GH. Oral fluid therapy of Apache children with acute infectious diarrhoea. *Lancet.* 1972; 2:15-8.
- Sack DA, Chowdhury AMAK, Eusof A, et al. Oral hydration in rotavirus diarrhoea: a double blind comparison of sucrose with glucose electrolyte solution. *Lancet.* 1978; 2:280-3.
- Pizarro D, Posada G, Mata L, Nalin D, Mohs E. Oral rehydration of neonates with dehydrating diarrhoeas. *Lancet.* 1979; 2:1209-10.
- The WHO Diarrheal Diseases Control Programme. *WHO Weekly Epidemiol Rec.* April 20, 1979; 54(16):121-3.
- Harrison HE. The treatment of diarrhea in infancy. *Pediatr Clin North Am.* 1954; 1:335-48.
- Finberg L. The role of oral electrolyte-glucose solutions in hydration for children — international and domestic aspects. *J Pediatr.* 1980; 96:51-4.
- Bart KJ, Finberg L. Single solution for oral therapy of diarrhoea. *Lancet.* 1976; 2:633-4.
- Nichols BL, Soriano HA. A critique of oral therapy of dehydration due to diarrheal syndromes. *Am J Clin Nutr.* 1977; 30:1457-72.
- NCHS growth curves for children birth — 18 years, United States. Hyattsville, Md.: National Center for Health Statistics, 1977. (DHEW publication no. (PHS)78-1650).
- Santosham M, Sack RB, Froelich J, et al. Biweekly prophylactic doxycycline for travelers' diarrhea. *J Infect Dis.* 1981; 143:598-602.
- Yolken RH, Wyatt RG, Zissis G, et al. Epidemiology of human rotavirus types 1 and 2 as studied by enzyme-linked immunosorbent assay. *N Engl J Med.* 1978; 299:1156-61.
- Flewett TH, Bryden AS, Davies H. Virus particles in gastroenteritis. *Lancet.* 1973; 2:1497.
- Finberg L. Parenteral fluid and electrolyte therapy. In: Gillis SS, Kagan BM, eds. *Current pediatric therapy 9.* Philadelphia: WB Saunders, 1980:761-7.
- Haddow JE, Cohen DL. Understanding and managing hypernatremic dehydration. *Pediatr Clin North Am.* 1974; 21:435-41.
- Rosenfeld W, deRomana GL, Kleinman R, Fineberg L. Improving the clinical management of hypernatremic dehydration: observations from a study of 67 infants with this disorder. *Clin Pediatr.* 1977; 16:411-7.
- American Medical Association. *Sample criteria for short-stay hospital review.* Washington, D.C.: Government Printing Office, 1976:653-978.
- Oral therapy for acute diarrhoea. *Lancet.* 1981; 2:615-7.