Oral rehydration and maintenance of children with rotavirus and bacterial diarrhoeas

D. R. NALIN,' M. M. LEVINE,' **L.** MATA,' C.DE CESPEDES,[4] **W.** VARGAS,[5] C. LIZAN0,[6] **A. R. LORIA,**[7] **A.** SIMHON,[a] & **E.** MOHS°

To determine whether oral glucose-electrolytes therapy could be adapted with equal success to infants with diarrhoea of bacterial and viral etiologies, oral glucose-electrolytes therapy was studied in a setting where all dehydrated infants with rotavirus or bacterial diarrhoeas routinely received intravenous fluids. Fifty-eight of 62 infants with acure diarrhoea and 5-10% dehydration who received a simple oral therapy regimen, were successfully rehydrated with oral therapy alone, without any intravenous fluids. The success rate of oral therapy was ***similar among diarrhoea patients infected with rotavirus or bacterial pathogens. Oral therapy is safe and effective for the treatment of viral and bacterial diarrhoea in infants with 5-10% dehydration.***

Rotaviruses are now recognized as a common cause of infant diarrhoea the world over ***(1-3)*** and recently a defect in glucose-coupled sodium absorption was reponed in piglets with rotavirus diarrhoea (4). In the present study we compared the clinical efficacy of oral glucose—electrolyte therapy in infants with diarrhoeas of different etiologies in order to determine whether the absorption defect induced by rotaviruses might reduce the efficacy of oral therapy in rotavirus patients as compared to patients with bacterial diarrhoeas.

MATERIALS AND METHODS

The study included 62 Costa Rican children 3-15 months old (36 male, 26 female ; 95 % < I year of age, mean age 5.5 months) with diarrhoea and 5-10 % dehydration. Parental consent was obtained. Hospital practice was to treat all such children with intravenous fluids. Histories from parents indicated a mean of 2.9 days of profuse watery diarrhoea, with vomiting in 88 % of cases. All patients had some signs of dehydration, including reduced skin turgor, sunken eyes, dry mouth, lack of tears, and depressed anterior fontanelle. Fever was present in 88% (mean 38.3°C). All but one child had a palpable, usually thready, rapid pulse (141 -1-.3 beats/min ; all figures in text given as means ± SE). Blood pressure, obtained by the " flush " technique, was between .5. 33 and 9.33 kPa (40 and 70 mmHg) in 31%, representing the most severely dehydrated infants. Deficits in weight-for-age (Gomez classification) were similar to those in the general population (33% 1st degree, 20% 2nd ***degree,*** and 1 % 3rd degree) **(5)** .

Oral therapy method

The oral formula used was that recommended by the World Health Organization 6), containing (g/1) glucose, 20 ; NaCI, 3.5 ; $NaHCO_3$, 2.5 ; KCI, 1.5. The chemical composition was analysed before use. Therapy was begun after the infants **had** been weighed and specimens of blood and stool obtained. The success rate of oral therapy depends on several factors, including the adequacy of ingested volumes of oral solution in relation to fluid losses in

Assistant Professor of Medicine and Chief, Physiology Section, Center for Vaccine Development (CVD), School of Medicine, University of Maryland. Baltimore, MD 21201, USA.

' Associate Professor of Medicine and Director, CVD, School of Medicine, University of Maryland.

' Director, Institute for Health Research, University of Costa Rica **(INISA), San** Jose, Costa Rica.

' Biochemistry Research Laboratory, National Children's Hospital (NCH). San Jose, Costa Rica.

Paediatrician, NCH.

' Chief of Laboratories, NCH.

' Clinical Biochemist, NCH.

' Technician. INISA.

Director, NCH.

stool and vomitus. In order to identify any differences in success rates among different etiological groups, meticulous care was taken to ensure that all infants received adequate volumes of oral solution, as well as the extra water needed to replace insensible losses (7-9). The oral solution and water were both warmed (37°C).

To initiate rehydration, infants received two bottles (400 ml) of oral solution, sip by sip, followed by one bottle of water (200 ml). This regimen was repeated until skin turgor became normal. Skin turgor was used as a bedside guide to the progress of therapy. When skin turgor became normal, the oral solution was discontinued, and infants then received half-strength milk formula 1.84 kJ/litre ; 200 ml every 4-5 hours.) After rehydration and transfer to milk formula, infants were taken off milk formula and given more oral solution *only* if diarrhoea continued *and* skin turgor again became abnormal. By 24 hours, and often earlier, most children's stools became semi-formed or pasty, and they were then advanced to full milk formula or to breast milk as tolerated. Nurses and auxiliaries administered the solution. If gastric distension developed, oral therapy was briefly slowed to avoid emesis. Children were permitted no more than 100 ml during any 20-min period.

It is important that rehydration should be well under way within the first 6 hours after initiating therapy. Since the oral solution is not entirely absorbed, and diarrhoea continues during rehydra-tion, the total volume of oral therapy and free water (or milk) given during the first 6 hours was twice the initial fluid deficit (estimated as percentage dehydration X weight) ; this averaged 580 ± 75 ml of oral solution or 230 ± 15 ml of water. Since most infants were not entirely rehydrated by 6 hours after initiating therapy, milk was generally withheld for 6 hours or more to avoid delayed gastric emptying during oral rehydration, but 23 infants who were normally hydrated before 6 hours received an average of 200 ml of milk formula during this period. The average ratio of volume of oral solution to other fluids (water amd milk) during the first 6 hours was two to one. Total 24-hour oral intake was 1.6 ± 0.1 litres.

Infants were weighed 6-hourly for the first 24-hours and daily thereafter. Urine bags, disposable diapers, and emesis sheets were weighed before and after use, to quantify losses in boys. In girls, the balance was estimated from oral intake and weight change. Insensible losses were estimated as 30 g/kg per 24 hours plus 9.7 g/kg per 24 hours per degree Celsius above 36.7°C *(10).* Therapeutic progress was determined from balance data and serial changes in clinical signs, weights, haematocrits, plasma proteins, and serum electrolytes. Infants who failed to absorb sufficient oral fluid for rehydration were given intravenous fluids. About 113% of cases received antibiotics (ampicillin) for prolonged diarrhoea due to *Shigella.*

Emergency-room records were reviewed to evaluate the potential impact of oral therapy on intravenous fluid consumption.

Laboratory methods

On admission, and after 6 and 24 hours, venous blood, urine, and liquid stool specimens were collected for analysis. Plasma and stool proteins were measured by refractometry and by the Biuret technique, respectively, Na' and K' by flame photometry, Cl^- on a Butchler-Cotlove chloridometer, bicarbonate with a Natelson gasometric apparatus, glucose by the orthotoluidine method *(11),* osmo-larity on an Osmette freezing-point depression osmometer, and urea by colorimetry after treatment with urease and nesslerization *(12).* Stool pH was measured with Hydrion pH strips.

Aliquots of aspirated stool were plated on Ter-gitol-7 (with biphenyl tetrazolium chloride) *(13)* Salmonella-Shigella, thiosulphate-citrate bile salts (TCBS), MacConkey's and Mycosel agar media for isolation of Enterobacteriaciae, *Vibrio para-haemolyticus, Aeromanas,* yeasts and other agents.° Stool was placed in brain—heart infusion broth *containing* 0.5 % of bovine serum albumin, with penicillin and streptomycin, and frozen until tested for rotavirus by the ELISA technique *(14, 15).* After subculture on lysine—iron and triple sugar—iron agars, presumptive colonies of *Salmonella, Shigella;* and enteropathogenic *Escherichia coli* were identified by biochemical *and* agglutination tests with appropriate antisera (16). Diagnosis of entero-pathogenic *E. coli* serogroups was made by titration of the O antigen in boiled cultures. Two *E. coli* colonies from each child were transferred to Gely-sate— peptone nutrient agar with beef extract and stored in the dark at room temperature for 1-7 days until extracts were prepared and tested for heat-stable and heat-labile enterotoxins by the infant-mouse and passive-immunolysis techniques *(17, 18).*

' All the media used were from Baltimore Biological Labors-tory, Cockeysville, MD, USA.

Response to treatment

Successful rehydration with oral therapy alone, with no adverse complications, was achieved in 94 % of the infants. Efficacy of oral therapy was documented by improvement in clinical signs of dehydration, normalization of plasma proteins and haematocrits, and increased body weight (Table 1). Analysis of weight changes after rehydration indicated that 47 % of the patients entered with 7-.10% dehydration ; the average dehydration was 6 %. Post-rehydration haematocrit values indicated a high prevalence of incidental anaemia in the study patients.

Table 1. Progress of oral rehydration among 58 children admitted with acute diarrhoea

	Hours after start of study		
	0	6	24[a]
weight (kg)	6.2 ± 0.2	6.5 ± 0.2	6.6 ± 0.2
plasma proteins (g/l)	80 ± 1	66 ± 1	63 ± 1
haematocrit[b]	0.40 ± 0.006	0.32 ± 0.02	0.32 ± 0.007

[a] $P < 0.001$ for all changes.
[b] Haematocrit of 1.00 = 100 %

Most children drank the oral solution avidly. Skin turgor was normal by a mean of 7.3 ± 0.5 hours (6.9 hours in rotavirus patients). Eighty percent of children **regained over half their fluid deficit by 6 hours; 34 % were completely rehydrated and free of** significant diarrhoea by 6 hours, and 76 % were normal by 24 hours. Urine production averaged 1.2 ± 0.1 **ml/kg per hour during the first 24 hours (males, n = 29).**

Recurrent diminution of skin turgor necessitated additional oral therapy after 24 hours in 39% of cases, but only 23 % required more than 500 ml (mean, 700 ± 100 ml) after day 1. Two discharged infants returned, one 2 days later with continuing *Salmonella* **diarrhoea (without dehydration), the other after 2 weeks, with diarrhoea associated with a new pathogen.**

Some vomiting occurred during therapy in 63 % of cases, but the low total volume (169 ± 26 ml) and infrequent episodes (2.5 ± 0.4) precluded significant effects of emesis on results. Success rates among the different etiological groups (Table 2) were : rotavirus, 92% ; *E. coil* diarrhoea, 93%; idiopathic diarrhoea, 96%; *Salmonella and Shigella* diar-rhoeas, 100 %; these rates did not differ significantly.

Safety of therapeutic method

The safety of oral therapy was confirmed by rapid improvements in a wide range ofelectrolyte abnormalities present on admission, including (mmol/l) hyponatraemia (128 ± 4 in 24 % of cases), hypernatraemia (151 ± 1 in 23 %), hypokalaemia (3.0 ± 0. 1 in 27%) and increased anion gap (Table 3). By

Table 2. Infectious agents identified in stools of children with acute diarrhoea

Pathogen	% of cases
rotavirus	40.0
Escherichia coli	23.0
enteropathogenic serogroup	
nontoxigenic	11.3
toxigenic (ST)[a]	3.2
nonenteropathogenic serogroup	
toxigenic (ST)[a]	5.3
toxigenic (LT)[b]	3.2
Shigella (Groups B and D)	8.0
Salmonella (Groups B and E)	6.0
one or more agents	63.0
two or more agents	13.0
no viral or bacterial agent identified	37.0

[a] ST = heat-stable enterotoxin.
[b] LT = heat-labile enterotoxin.

Table 3. Changes in blood composition during treatment ($n = 57$; mean ± SE)

	Hours after start of study		
	0	8	24
Na' mmol/ll	140 ± 1,2	137 1.0	137 ± 0.8
K' (mmo1/1)	4.0±0.1	3.8±0.1	3.9±0.11
Cl - (mmol1/1)	114 ± 1.8	112 ± 1.5	107 t 1.6'
HCO-, Immol/tl	18 ± 0.7	21 ± 0.9	23 ± 0.8
glucose immol/ll	8.55 ± 0.23	5.77 ± 0.83	5.38±0.18
urea (mmol/l)	5.18±0.87	3.93±0.30	2.33±0.20°
osmolarity`	290±3.4	278±2,4	273±8.8a
anion gap	13 ± 1.3	11 ± 1.3	10 ± 1.2

• $P < 0.02$.
° $P < 0.001$.
Milliosmoles *per* litre.

24 hours ail sodium levels had improved; all were then normal except for 5 hyponatraemic cases. Relative HCO_3 and K' deficits, with serum HCO_3^- below 25 mmol/l in 62% of cases and serum K' under 3.3 mmol/l in 18%, persisted after 24 hours of therapy. Mean total balance for 24 hours (Table 4) was + 33 mmol for Na+ and - 10 mmol *(negative* balance) for K` in males (n = 31). Absorption in rotavirus and non-rotavirus groups was equal.

Table 4. 24-hour net balance in males with rotavirus and non-rotavirus diarrhoea (mean ± SE)˙

	Rotavirus (n.- 12)	non-rotavirus (n-91
weight after rehydration (kg)		
volume of (litres).	7.0 ± 0.4	6.0±0.8
stool	0.8 3 0.1	0.0 ± 0.1
total oral intake	1.7 ± 0.2	1.5 # 0.1
oral solution alone	0.9 ± 0.1	0.8 ± 0.1
amnia	0.1 t 0.05	0.04 ± 0.01
net water absorption °	+ 1.0 ± 0.2	+ 0.9 ± 0.1
urine	0,16±0.04	0.2 ± 0.04
Insensible losses	0.3 ± 0.03	0.3±0.03
weight gain (kg)	0.37±0.06	0.24±0.05
urinary excretion (mmol)		
Ns'	3±1	5±3
K'	4±1	6±5
net absorption (mmol)		
Na'	+41±7	+36±9
it-	-18±3	-12±2

' Males with non-rotavirus diarrhoea included 5 enteropathogenic E. coil and 4 idiopathic. Nat N.' and H,0 absorption did not differ significantly between the groups. The smell difference between actual weight change sod Calculated total balance reflects net weight loss due to dietary energy deficiency during diarrhoea.
° Net water absorption = net gut balance, or difference volumes of ingested water and water the lost in stool between vomitus. and

Mean diarrhoea rate in males was 5.2 ± 0.05 ml/ kg per hour for the first 24 hours after admission. Stool Na' and K' levels were consistent with the relatively low diarrhoea rates *(19)* (Table 5). Stool pH averaged 6.2 ± 0. 1, and was between 5 and 6 in 67 T. of cases, presumably due to neutralization of intestinal bicarbonate by acid products of bacterial metabolism. Stools contained a significant quantity of unidentified, presumably organic, cations. Para-*sites'(Ascaris)* were found in only two cases.

Table 5. Changes in composition of diarrhoea) stools *(mean* ± SE) during first 24 hours

	Hour* Cher start of study		
	0 (n-43)	6 (n-39)	24 (n-27)
Net)mmol/l	30±4	50±5'	43±6
K• mmol/l)	32±2	38±2˚	29±3
CI- mmol/l)	32±7	59±6˚	37±11
glucose mmol/ORV'	28.7±6.9	23.3t5.7	0.7 ± 4.7
NRV°	15.2±3.7	14.7±3.3	9.9±3.2
proteins (g/i) (n- 18)	3.95 ± 0.41	1.75±0.23°	3.41 0.75
osmolarity'	339±17	314±25	329±17

• P<0.02.
° P c 0.08.
° RV - Infants with rotavirus Infection,
"MV - infants with diarrhoea due to an etiology other than rotavirus.
• MIIlosmoles per litre,

The proportion of rotavirus patients with stool glucose levels over 27.75 mmol/l was 59% and 44% at 0 *and* 6 hours, respectively, and differed significantly from the proportion of non-rotavirus patients in the same category (27% and 17% for rotavirus cases at 0 and 6 hours, $P = 0.05$) (Table 5). However, net balance data and clinical response clearly indicated absorption sufficient to correct deficits in all etiological groups (Tables 1, 4).

Therapeutic failures

Four patients admitted during the first 2 weeks of the 10-week study required intravenous fluids, including one who was hypotensive on arrival and semiconscious with pneumonia, had a temperature of 41°C, alkalosis, and hypocalcaemia with tetanic spasms due to home therapy with Alka-Seltzer. One patient had glucose malabsorption *(20)* with a stool glucose level equal to that of the oral solution ; his diarrhoea recurred after feeding with 350 ml of 50 g/ litre (278 mmol/l) glucose within 4 hours in convalescence Two other patients who refused the oral solution arrived with severe hyponatraemia and inappropriately large volumes of urine of low specific gravity during dehydration ; early recognition and intensive oral therapy led to success in 13 similar cases. Of the 4 oral therapy failures, 2 were malnourished, 2 had 6% and 2 had 10% dehydration on admission. Since these proportions do not differ significantly from those of the study popula-

Lion. nutritional state and degree of dehydration appear not to correlate with treatment failure. There were no deaths.

Emergency-room survey

During the two months preceding the study, 212 children under 15 months of age (24 % under 3 months) were treated for diarrhoea with dehydration averaging 3-5 %, Of these, 90 % received intravenous fluids averaging 640 ± 50 ml per patient, although only 6% had dehydration greater than 5 %. The duration of emergency-room treatment was less than 1 day in 36 % and averaged 1 day in 64 %; 3 % were hospitalized further and 5% were readmissions with recurrent dehydration.

DISCUSSION

The results indicate that oral therapy is safe and effective for rehydration in most infants with 5-10 % dehydration due to viral or bacterial diarrhoeas. The few failures (6 %) must still be recognized and given the intravenous fluids they require. The regimen we used adequately corrected both hypo-and hypernatraemia. The persistent $_{HCO3-}$ and K-deficits and the high K^- concentration in stools indicate the need to test solutions with higher HCO_3-and K' concentrations (21).

The higher stool glucose concentration in rotavirus patients may be associated with the defect in glucose-coupled Na' transport reported in piglets infected with rotavirus *(4)*. Nevertheless, rotavirus patients absorbed enough oral solution for successful rehydration. The patchy intestinal lesions in rotavirus infections (22) suggest that the absorptive capacity of unaffected vinous cells may be adequate to ensure net absorption; this could explain the efficacy of the oral solution in rotavirus patients.

The demonstration of satisfactory rehydration and correction of initially high or low serum Na' levels indicates that, as with intravenous Dacca solution (133 mmol/l Na') for children (23), infants can tolerate the oral solution with 90 mmol/l of Na' if water is given freely orally' to generate adequate urine and to replace insensible water losses. Total net balance is more important than electrolyte concentrations of the oral solution alone. Assuming that in pre- and postadmission diarrhoea the stools had similar composition, the preadmission Na^- deficit would average 16 mmol. Thus the mean net Na^-absorption (Table 4) approximates that associated with a normal energy diet of children fed cow's milk (24), even ignoring a correction for Na^-losses in sweat.

Comparison of study results with emergency-room records indicated that, in addition to the 94 % of significantly dehydrated patients treatable with oral therapy, many others who received intravenous fluids for minimal dehydration could also have benefited from oral therapy, with reductions in costs, physician time, and patient trauma. The results may well be applicable to the treatment of diarrhoea in developed as well as developing countries, and may have application in homes as well.

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RESUME

REHYDRATATION MR VOLE ORALE ET MAINTIEN DE L'EQUILIBRE CHEZ LES JEUNES ENFANTS ATTEINTS DE DIARRHEE A ROTAVIRUS OU A BACTERIES

Pour apprécier l'efficacité de la thérapie orale scion le type de diarrhée (á rotavirus ou bactérienne), une etude a Eté faite sur 62 jeunes enfants costa-riciens présentant une deshydratation de 5 á 10 % provoquée par une diarrhée aigué et á qui une solution de glucose-electrolyte a été administrée par voie orale. Le liquide utilise avail la formule suivante (grammes par litre d' eau) : NaC1: 3,5 ; KC1: 1,5 ; $NaHCO_3$: 2,5 ; glucose : 20. La perte de liquide a Eté estimée en multipliant le poids de]'enfant 8 l'admission par le pourcentage de déshydratation apprécié en fonetion de signes cliniques. Les liquides administres par voie buccale pouvant ne pas étrc entierement absorbes tans que dure la diarrhée, les bébés ont rev une quantité de solution orale et d' eau naturelle représentant au total le double de la pene de liquide estimée. Apres deux biberons de solution de 200 ml chacun, un biberon d'eau ordinaire de méme contenance (200 ml) ¿ tail administré et ainsi de suite. Le regain d'élasticite de la peau a permis d'apprécier empiriquement la réhydratation, et le regime thérapeutique décrit (2 + 1) a *été* maintenu jusqu'i ce que I'elasticité cutanée soit redeve-nue normale ; on a alors censé d' administrer la solution et recommence á alimenter le nourrisson. Les données recueillies quant au bilan liquide adminis-tré/liquide perdu et toute la serie de controles portan sur le poids, l'hématocrite, les protéines du plasma et les electrolytes sériques ont permis de constater que cette tres simple méthode d' administration orate de liquide avait tres rapidement remédié á la déshydratation dans 94 % des cas. Les résultats n'ont pas presenté de differences significatives selon que les nourrissons souffraient de diarrhée due a des rotavirus ou *A* des bactéries, si ce n'est un accroissement cliniquement peu important de l' excrétion de glucose dans les selles lorsqu'un rotavirus était en cause. Les bébés ont répondu également bien au traitement quels que soient leur état nutritionnel et les anomalies des electrolytes présen-tees lors de l'admission. Jusque-bk tout nourrisson chez qui était constatée une déshydratation du méme ordre que chez ceux soumis á l'étude faisaient]'objet d'un thérapie intra-veineuse. En obtenant le résultat voulu chez 94 % des sujeta sans avoir á recourir it cette derniére méthode, l'étude a montré clairement la valeur de la thérapie orale, qui permet de réduire A la fois le coat du traitement et ses effets traumatisants dans les cas de diarrhée infantile.

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