Oral rehydration in infantile diarrhoea

Controlled trial of a low sodium glucose electrolyte solution

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SUMMARY The paper describes the first controlled trial of an oral glucose electrolyte solution designed on the basis of the optimum pathophysiological needs for rehydration in infantile diarrhoea. The solution, having a sodium concentration of 50 mmol/l, was tried in a group of 20 infants with moderate to severe dehydration due to acute diarrhoea and was compared with a matched group of 19 infants predominantly under 2 years of age taking a 'standard' oral solution with a sodium concentration of 90 mmol/l. They could be hydrated as well with a low sodium oral solution alone as with the standard solution. Intravenous fluid was not required in either group. The group treated with the high sodium 'standard' solution appeared to develop hypernatraemia and/or periorbital oedema more frequently than the other group. Also, the low sodium solution eliminated the need for additional free water orally.

Development of oral hydration for acute diarrhoeal diseases has emerged as a major therapeutic advance (Pierce *et al.*, 1968; Hirschhorn *et al.*, 1968, 1972, 1973; Sack *et al.*, 1970; Nalin *et al.*, 1970; Mahalanabis *et al.*, 1973, 1974; *Lancet*, 1975). A single universal oral hydration solution having a sodium concentration of 90 mmol/l has been recommended by WHO/UNICEF (Treatment and Prevention of Dehydration in Diarrhoeal Diseases, 1976) for rehydration, 'in all age groups with acute diarrhoea of all causes'. This universal oral hydration solution emerged largely from the studies in adult patients with acute cholera and has subsequently been used in children. It has been shown that the average faecal sodium concentration in infantile diarrhoea is about 56 mmol/l as against 101 and 140 mmol/l in children and adults with cholera respectively (Mahalanabis *et al.*, 1970). Furthermore, the possible risk of hypernatraemia after the use of such a solution in infants has prevented its wider acceptance by paediatricians.

This study was designed (a) to evaluate the efficacy and safety of an oral solution with a lower sodium concentration (50 mmol/l) similar to the mean faecal sodium concentration in infantile diarrhoea, (b) to attempt complete hydration of infants with moderate

and severe dehydration with oral solution alone, and (c) to investigate the possible risk of salt overload in infantile diarrhoea with the oral solution advocated by WHO/UNICEF.

Material and methods

Infants and children aged 4 months to 4 years, admitted with a history of acute watery diarrhoea with or without vomiting, and with moderate to severe dehydration as judged by clinical examination (i.e. moderate to marked loss of skin turgor, sunken eyes, dry mucous membrane, tachycardia with or without a feeble pulse), were included in the study. They were randomly assigned to either of two treatment groups, A and B.

Children in group A were hydrated by an oral solution (solution A) similar to the one advocated by WHO/UNICEF (Treatment and Prevention, 1976) having the following composition: Na^+ 90, K^+ 15, Cl^- 75, HCO_3^- 30 mmol/l (90, 15, 75, 30 mEq/l), and glucose 90 mmol/l (1621 mg/100 ml). Children in group B were treated by an oral solution (solution B) containing Na^+ 50, K^+ 15, Cl^- 50, HCO_3^- 15 mmol/l, glucose 170 mmol/l (3063 mg/100 ml). Both solutions had a calculated osmolality of 300 mOsm/l.

Before treatment the child was weighed nude on

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a balance with a sensitivity of 1 g. A nasogastric tube was introduced, the stomach aspirated, and intra-gastric drip of either solution was started. Solutions A and B were given at approximately 10 ml and 12.5 ml/kg per hour, respectively, until complete clinical hydration was achieved. Those children who had further diarrhoea were given the same solutions orally as drinks to replace stool losses. Patients in group A were actively encouraged to drink additional water after 4 hours of hydration. Allowance of free water in these children was dictated by ethical considerations and our desire to conform to the recommendations of WHO/UNICEF (Treatment and Prevention, 1976).

Initial hydration was usually achieved within 12 to 24 hours, after which patients were allowed dilute milk and/or breast milk; low lactose milk formula not being available. Whole cows' milk was restored usually within 3 days of admission. Older children were allowed components of adult diet within 24 to 48 hours. All patients received tetracycline hydrochloride 50 mg/kg body weight per day for 4 days, in accordance with the prevailing practice in the paediatric unit where the study was conducted.

Clinical features, plasma specific gravity, and haematocrit were recorded on admission, at 6 hours, after initial hydration, 48 hours after admission, and on recovery. Recovery was defined as a time when a stable body weight was attained after diarrhoea had stopped. This usually took 5 to 6 days. Plasma electrolytes were estimated in triplicate from frozen samples on admission, after initial hydration, and at recovery in a flame photometer, plasma CO₂ combining power by a Van Slyke volumetric apparatus, and plasma specific gravity by a temperature compensated refractometer (T. S. Meter^{-R}, American Optical Co.).

Stool samples were examined routinely for the presence of reducing substance using Benedict's qualitative reagent. Methods for isolation of enteropathogens have already been described (Sack *et al.*, 1970).

Results

Of the 39 infants, 19 received solution A (group A) and 20 solution B (group B).

Nutritional status. Table 1 shows that except for 2 children in group A and 1 in group B, all had varying degrees of malnutrition. Clinical kwashiorkor was present in 3 in group A and 2 in group B.

Enteropathogens. Known enteropathogens were shown only in 4 cases of group A; three were enteropathogenic *E. coli* (EPEC) type 0.128: K67

(B12) and the fourth *Vibrio cholerae* El tor (Inaba). In 5 patients in group B enteropathogens were isolated; three were EPEC type 0.128: K67(B12), and two were *V. cholerae* El tor (one Inaba, and one Ogawa). Lack of facilities prevented the search for reovirus as an aetiological agent.

Clinical features. Table 2 shows that the clinical features were comparable in the two groups of patients. 93% of the children had altered sensorium (i.e. drowsy, or drowsy with irritability to touch, or comatose) of whom 10% had frank convulsions on admission. Hypernatraemia (Na⁺>150 mmol/l) on admission was noted in 2 in group A and 1 in group B (Fig.). Neurological manifestations were absent in all of the children with hypernatraemia on admission; however, one had a history of seizures before admission. Per cent weight gain, and biochemical values recorded on admission and at various points during recovery (Table 3, Fig.) showed no significant differences between the two groups.

Table 1 Nutritional status: body weight as percent of expected weight (Harvard mean), and evidence of sodium overload in the various nutritional groups*

Study group	Normal nutrition (>80%) (n)	Mild malnutrition (71-80%) (n)	Moderate malnutrition (61-70%) (n)	Severe malnutrition (≤60%) (n)
A	2 (0, 2)†	4 (0, 1)	8 (2, 3)	5 (1, 1)
B	1 (0, 0)	3 (0, 0)	6 (0, 1)	10 (1, 2)

*3 patients in group A and 2 in group B were suffering from kwashiorkor.

†First figure in parentheses represents the number with hypernatraemia persisting or developing after oral hydration, and the second figure the number developing periorbital oedema after treatment.

Table 2 Comparison of the two study groups hydrated with two different oral fluids

	Group A* (n=19)	Group B (n=20)
Median age (yr) (range)	0.75 (0.33-4.0)	0.76 (0.33-1.91)
Age distribution (yr)		
≤0.5	6	7
0.5-1.0	6	8
1.0-2.0	4	5
2.0-4.0	3	0
Findings on admission (mean ± SE)		
Pulse rate	143 ± 6	148 ± 7
Rectal temp (°C)	38.5 ± 0.28	38.6 ± 0.28
Systolic BP (mmHg)	91 ± 2	88 ± 2
Duration of diarrhoea before admission (d) (mean ± SE; range)	4.6 ± 0.8 (0.5-10)	3.3 ± 0.6 (1-10)
Body weight after recovery (kg) (mean ± SE; range)	6.30 ± 0.45 (3.40-10.48)	5.26 ± 0.23 (3.43-7.19)
Mean time required for initial hydration (h)	16.7	19.4

*Groups A and B were hydrated by solutions A and B respectively.

Table 3 Body weight and biochemical parameters (mean $\pm$ SE) on admission and during recovery in the two study groups at indicated times

Study groups	On admission	6 hours after admission	After complete initial hydration	48 h after admission	At recovery
Weight gain (%)*					
A		2.78 $\pm$ 0.58	5.31 $\pm$ 0.63	7.31 $\pm$ 0.87	9.24 $\pm$ 1.1
B		2.61 $\pm$ 0.45	6.21 $\pm$ 0.41	7.62 $\pm$ 0.65	9.63 $\pm$ 0.71
Plasma specific gravity					
A	1.0270 $\pm$ 0.0008	1.0254 $\pm$ 0.0007	1.0226 $\pm$ 0.0005	1.0229 $\pm$ 0.0006	1.0235 $\pm$ 0.0004
B	1.0276 $\pm$ 0.0008	1.0263 $\pm$ 0.0007	1.0229 $\pm$ 0.0005	1.0234 $\pm$ 0.0007	1.0230 $\pm$ 0.0006
Haematocrit (%)					
A	38.4 $\pm$ 1.0	35.3 $\pm$ 1.1	30.7 $\pm$ 0.7	32.0 $\pm$ 0.8	31.2 $\pm$ 0.9
B	38.5 $\pm$ 1.1	36.9 $\pm$ 1.2	30.9 $\pm$ 1.1	31.8 $\pm$ 1.2	31.1 $\pm$ 1.1
Sodium (mmol/l)					
A	136.3 $\pm$ 3.1	—	139.2 $\pm$ 3.2	—	138.5 $\pm$ 2.6
B	132.4 $\pm$ 2.7	—	137.9 $\pm$ 2.3	—	139.2 $\pm$ 2.3
Potassium (mmol/l)					
A	3.1 $\pm$ 0.2	—	2.9 $\pm$ 0.3	—	3.9 $\pm$ 0.2
B	3.4 $\pm$ 0.2	—	3.7 $\pm$ 0.3	—	4.3 $\pm$ 0.1
Bicarbonate (mmol/l)					
A	8.6 $\pm$ 0.6	—	16.2 $\pm$ 0.6	—	23.0 $\pm$ 0.7
B	7.5 $\pm$ 0.5	—	14.8 $\pm$ 0.6	—	23.2 $\pm$ 0.8

*Expressed as percent of recovery body weight.

Fig. Plasma sodium values on admission and during recovery.

Results of treatment. All the children in both groups were successfully hydrated orally and none required intravenous therapy. Table 4 shows the rate and amount of oral fluids given to each group of patients. In group A 2 patients were hypernatraemic on admission (Fig.), of whom one became normonatraemic after treatment, while the other remained hypernatraemic until recovery; and 2 normonatraemic children on admission developed hypernatraemia after treatment. However, none of these

patients showed neurological manifestations. Detailed clinical and biochemical information on the patients with persistent hypernatraemia is given in Table 5. In group A periorbital oedema was noted in 7 patients after initial hydration, which regressed over a period of 1 to 5 days. In group B hypernatraemia on admission was noted in one case, which persisted up to the end of initial hydration but returned to near normal at the time of recovery (Fig.). This child also showed no neurological manifestation. In 3 cases mild periorbital oedema unrelated to hypernatraemia was noted but regressed over a period of 1 to 2 days.

There were 2 late deaths (1 pneumonia, 1 septicæmia) in group B. Both were kwashiorkor babies, with wasting, pitting oedema, typical hair and skin changes. 2 patients in group B and 1 in group A had abdominal distension with hyperperistalsis on

Table 4 Amount of oral hydration fluid and water administered

	Group A	Group B
Intragastric drip over first 6 h (ml/kg per h)		
Mean $\pm$ SE	10.3 $\pm$ 0.41	13.9 $\pm$ 0.53
Maximum	13.5	17.6
Amount of oral fluid required for initial hydration (ml/kg) (mean $\pm$ SE; range)	133.2 $\pm$ 8.3 (98–229)	211.5 $\pm$ 9.3 (159–291)
Amount of additional oral solution needed after initial hydration (ml/kg) (mean $\pm$ SE) (n=number who needed it)	58.4 $\pm$ 19.4 (n=7)	77.3 $\pm$ 25.3 (n=9)
Water intake during initial hydration (ml/kg) (mean $\pm$ SE)	74.6 $\pm$ 5.8*	Nil

* Started after 4 hours of hydration.

Table 5 Clinical and biochemical data of cases with persistent hyponatraemia

Case no. (group)	Age (yr)	Duration of diarrhoea before admission (d)	Nutritional status (body wt as % of Harvard mean)	Degree of dehydration (%)	Rectal temp on admission (°C)	Diet		Neuro- logical manifest- ations	Peri- oral oedema after hydration	Persis- tence of diar- rhoea after initial hydra- tion	Intake of fluids (ml/kg)		Water* up to initial hydra- tion
						Before admission (history inadequate)	After hydration				Up to initial hydra- tion	After initial hydra- tion	
1 (A)	1.08	1	61	6	39.2	All received cows' milk in various forms. Case 3 also had breast milk	Cows' milk 2:1 with a changeover to whole cows' milk within 3 d; Case 2 was also given solid diet	None	None	None	118	Nil	101
2 (A)	1.5	4	63	10.5	38.9			Present	Yes	Yes	119	23	75
3 (A)	0.41	5	50	9.5	38.6			None	Yes	Yes	128	50	61
4 (B)	1.0	1	42	11.6	39.3			None	Yes	Yes	268	Nil	Nil

Plasma specific gravity											
Sodium (mmol/l)†				Potassium (mmol/l)†				Bicarbonate (mmol/l)†			
Ad	Hy	Rec	Ad	Hy	Rec	Ad	Hy	Ad	Hy	Rec	Ad
134	152.5	152.5	2.2	3.25	3.5	9.0	16.4	20.6	1.024	1.025	1.025
155	155	160	2.0	2.0	3.5	6.4	12.3	18.2	1.022	1.021	1.022
147.5	155	150	3.5	4.2	4.0	7.3	15.2	—	1.018	1.018	1.018
157.5	157.5	152.5	3.25	3.75	3.75	8.3	14.4	23.6	1.022	1.022	1.022

*Started after 4 hours of hydration.
†Plasma levels: Ad = admission; Hy = initial hydration; Rec = recovery.

admission but all 3 responded to oral hydration. A significant amount of glucose in the stool was found only in 2 children hydrated with the low sodium oral solution containing a relatively higher amount of glucose, but it did not interfere with oral rehydration. Vomiting, which is not uncommon during the initial phase, also did not prevent successful hydration.

Discussion

This is the first controlled study using an oral glucose electrolyte solution containing an optimum concentration of sodium designed in accordance with the pathophysiological needs (Darrow, 1946; Darrow *et al.*, 1949) of hydration therapy in infantile diarrhoea.

We have shown that comparable groups of infants predominantly under 2 years of age, with moderate to severe degree of dehydration, can be adequately hydrated with either solution alone. A steady intragastric drip and prior aspiration of stomach contents contributed to these satisfactory results from oral therapy even in those with severe dehydration. Although stool volumes could not be measured during therapy, careful clinical evaluation, repeated weighing of the infant, and sequential measurement of plasma specific gravity and haematocrit were deemed adequate indices of favourable response to oral therapy.

Previous studies have shown a significant rise in serum sodium in eight paired observations (Hirschhorn *et al.*, 1972), and periorbital oedema in 3 out of 17 infants (Hirschhorn *et al.*, 1973) treated with an oral solution similar to solution A, but no frank hypernatraemia was reported. Although no significant difference was found in this study for the development of hypernatraemia and/or periorbital oedema between the two groups, nevertheless children treated with a higher salt solution showed a trend towards developing these complications more frequently in spite of persistent efforts to administer water freely by mouth.

Several factors may have contributed to the persistence of hypernatraemia in these children. They were all young (Table 5) and were febrile on admission. The only hypernatraemic child who became normonatraemic after therapy was relatively older (3.74 years). No significant relationship between the nutritional status and persistence of hypernatraemia was observed (Table 1). In an effort to combat undernutrition, we introduced full strength cows' milk formula early, leading to varying degrees of osmotic diarrhoea in these children presumably due to temporary lactase deficiency (Chatterjee *et al.*, 1977) which further

contributed to hypernatraemia (Fordtran, 1973). Another important factor was that the majority of the children, including those who remained hypernatraemic, had low levels of serum potassium even in the presence of acidosis on admission, reflecting low total body potassium. This is known to cause sodium retention from the administered fluid, particularly if it is deficient in potassium (Cheek, 1956; Katcher *et al.*, 1953). It is notable that the group having high sodium oral solution received comparatively less potassium with respect to sodium than the other group. Although it would have been useful to investigate the response of the kidneys to salt overload in these children, ethical considerations prevented us from submitting them to any salt loading test when they had just recovered from severe acute diarrhoea.

Solution B with a lower sodium concentration is not only as effective as the recommended universal solution but also eliminates the need to ensure additional free water intake, thus rendering treatment much simpler, and its use reduces the risk of salt overload particularly under less stringent clinical supervision. Although none of the patients with persistent hypernatraemia manifested any central nervous system signs, this finding and also the frequent occurrence of periorbital oedema suggest caution in using high sodium oral hydration solutions in infants under 2 years of age.

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