Randomised double blind trial of hypotonic oral rehydration solutions with and without citrate

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Abstract

Hypotonic oral rehydration salts solutions (ORS) have been proved to be better than isotonic solutions with respect to water absorption. To establish whether a base precursor is essential in the composition of a hypotonic ORS with improved absorption properties, a randomised double blind clinical trial was conducted comparing two formulas of hypotonic ORS, each with an osmolality of 224 mmol/l, with or without citrate, in a group of 107 children admitted to hospital with acute diarrhoea. The two solutions were effective in the correction of dehydration and there was no difference between the treatments in the duration of diarrhoea. The patients receiving the hypotonic ORS with citrate consumed less of the solution, however, and their metabolic acidosis was corrected earlier. It is concluded that citrate is clinically advantageous in a hypotonic ORS, but a hypotonic formula without a base precursor is also effective. (*Arch Dis Child* 1994; 70: 44-46)

Oral rehydration therapy has been a significant advance in the treatment of diarrhoeal dehydration in developing countries. Although it has also gradually been accepted in developed countries, the optimum composition for an oral rehydration salts solution (ORS) in Europe and the USA is still controversial.¹⁻⁵ Findings from perfusion studies in infected rats and in human volunteers have indicated that hypotonic rather than isotonic solutions are optimal for the absorption of water and sodium and are therefore recommended for clinical use.⁶⁻⁹ A hypotonic oral rehydration solution with a sodium concentration of 60 mmol/l and an osmolality of 224 mmol/l has been compared with a commercially available oral rehydration solution with an osmolality of 304 mmol/l and it was found that the hypotonic solution was better than the isotonic solution in the treatment of acute diarrhoeal dehydration in young children.¹⁰

The need for bicarbonate or a base precursor in the ORS has also been questioned.¹¹ A simple salt-sugar solution would be easier and less expensive to prepare, but historically the inclusion of a base has been regarded as important or even critical for the enhanced absorption of sodium and water and for the correction of acidosis. Again, studies in rats indicate that the addition of bicarbonate or a base precursor does not have a significant effect on intestinal water and electrolyte

absorption, and, at a high concentration, bicarbonate may even reduce absorption in the case of intestinal secretion.^{3 12 13} Although an ORS with bicarbonate or a base precursor appears to hasten recovery from acidosis, this may be of little clinical importance.¹⁴⁻¹⁶

Having established the excellent clinical performance of a hypotonic solution (osmolality 224 mmol/l), we wanted to evaluate the role of a base precursor using a solution of the same osmolality but without citrate for the treatment of diarrhoeal dehydration.

Patients and methods

The study protocol was approved by the ethical review committee of the health care centre of Helsinki. Informed parental consent was obtained for all patients enrolled in the study.

The study was carried out at the Aurora Hospital, Helsinki, between January 23 and July 20, 1992. Infants less than 36 months of age admitted to hospital for acute diarrhoea (duration five days or less before admission) were included in the study. Patients with serum sodium concentrations less than 130 mmol/l or greater than 155 mmol/l were to be excluded. One infant with an initial sodium concentration of 129 mmol/l on admission was enrolled, however, and was managed successfully with oral rehydration.

The eligible patients were randomised to receive either an oral hypotonic rehydration salts solution including citrate (citrate ORS) or a hypotonic ORS without a base precursor (non-citrate ORS). Table 1 gives the compositions of the two solutions. The solutions were prepared by the Helsinki city hospitals pharmacy and supplied as a dry powder, which was reconstituted in the ward with 500 ml water. The sachets containing the dry powder and the two solutions were identical in appearance, ensuring that the study was double blind.

An ORS was prescribed by the physician on duty after estimation of the degree of dehydration. The recommendation was to prescribe four thirds the estimated fluid deficit to be administered in the first six to eight hours. If

Table 1 Composition of the hypotonic ORS (mmol/l) used in the study

	Citrate ORS	Non-citrate ORS
Sodium	60	60
Potassium	20	20
Chloride	50	80
Glucose	84	64
Citrate	10	-
Total osmolality (mmol/l)	224	224

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Table 2 Characteristics of the patients on admission (mean (SD) values)

	Citrate ORS (n=54)	Non-citrate ORS (n=53)
Age (months)	13.5 (6.9)	16.9 (8.0)*
Duration of diarrhoea before admission (hours)	57.2 (30.4)	63.3 (33.0)
Acute weight loss (g)	311 (220)	364 (232)
Blood sodium concentration (mmol/l)	137 (3.7)	137 (3.6)
Blood base excess (mmol/l)	-7.5 (3.6)	-6.9 (3.9)

*p<0.02, two sample *t* test.

the child refused to drink, the solution was given through a nasogastric drip. After the initial rehydration the children were prescribed a minimum of 30 ml/kg/day of additional ORS. For continued vomiting and diarrhoea, the amount of ORS was increased according to their needs, as estimated by the physicians in the ward. Normal feeding for age was resumed after the initial six to eight hours of rehydration. Other fluids were given with food, including plain water, milk, and light juice.

The exact amount of ORS administered was recorded by the nurses in the ward. They also recorded all stools passed by the children (described as watery, loose, or solid), and all vomiting episodes. The weight was recorded on admission, after initial rehydration, and daily thereafter during their stay in hospital. Blood sodium, potassium, and the acid-base balance were determined on admission and daily thereafter during their stay in hospital. The sodium concentration in urine was determined from male patients in the morning after initial rehydration. A stool sample was taken during the stay in hospital for the detection of rotavirus using an enzyme immunoassay. A systematic search for other enteropathogens was not carried out.

All data were analysed using the Statistix 3.1 statistical analysis program for microcomputers. A two sample *t* test, rank sum two sample test, and the χ^2 test were used.

Results

Fifty four children received the hypotonic citrate ORS and 53 children received the hypotonic solution without citrate. Table 2 gives the characteristics of the two groups. The

two groups were comparable for duration of diarrhoea before admission to hospital, degree of dehydration, electrolyte balance, and acidosis. For no obvious reason, the patients who were randomised to the citrate ORS group were younger.

Sixty six (62%) of the 107 patients were positive for rotavirus and one patient was positive for adenovirus. Fourteen stool cultures were taken from various patients because of high fever, mucoid stools, or a history of travel; all were negative.

As the groups were not different with respect to weight loss on admission, the mean amounts of ORS given for initial rehydration therapy were almost identical: 557 and 563 ml respectively (table 3). There was no difference between the two groups in the weight gain after initial rehydration.

In contrast, the amount of ORS needed for maintenance differed between the groups. Therefore, the mean total consumption was 1335 ml in the citrate ORS group compared with 1643 ml in the non-citrate ORS group ($p=0.020$, rank sum two sample test, table 3). Of the 107 patients, three received intravenous fluids in addition to oral treatment; two were in the citrate ORS group and one in the non-citrate group.

There was no significant difference between the two treatment groups in the number of diarrhoeal stools (mean 9.7 and 7.7 in the citrate ORS and non-citrate ORS groups respectively), in the duration of the diarrhoea, or in the length of hospital stay (table 3). There was a small but non-significant difference in favour of citrate ORS in the duration of vomiting (table 3). The mean number of vomiting episodes was similar in the two groups (1.4 and 1.5 in the citrate and non-citrate ORS groups respectively, however).

The most significant difference between the treatments was in the duration of recovery from acidosis, which was significantly shorter in the citrate ORS group: the mean base excess in the morning after admission was -3.7 in the patients receiving the citrate ORS compared with -6.8 in those rehydrated with the non-citrate ORS ($p<0.001$). On the second morning after admission, however, the degree of acidosis was the same in the two groups (table 4).

The blood sodium and potassium concentrations were not different in the two treatment groups on admission and on subsequent days of treatment (table 4). The urinary sodium concentration after initial rehydration was also similar in the two groups (38.0 and 37.2 mmol/l in the citrate and non-citrate ORS groups respectively).

Discussion

In this clinical trial a hypotonic ORS with or without citrate performed almost equally for most measures of outcome. The two ORS solutions were efficient for rehydration. The hypotonic ORS with citrate corrected acidosis earlier than an almost similar ORS without citrate, however. Other than for the correction

Table 3 Outcome of the two treatment groups (mean (SD) values)

	Citrate ORS (n=54)	Non-citrate ORS (n=53)
Amount of ORS consumed in first 6-8 hours (ml)	557 (207)	563 (181)
Total amount of ORS consumed in the hospital	1335 (635)	1643 (740)*
Weight increase at time of discharge (g)	211 (229)	167 (212)
Duration of vomiting (hours)	17.1 (21.5)	25.4 (27.0)
Duration of diarrhoea in the hospital (hours)	38.0 (33.5)	41.8 (31.2)
Duration of stay in hospital (hours)	61.0 (34.5)	70.0 (34.9)

*p=0.020, rank sum two sample *t* test.

Table 4 Blood electrolyte and acid-base balance of the two treatment groups (mean values)

	Day 1 (admission) (citrate/non-citrate)	Day 2 (citrate/non-citrate)	Day 3 (citrate/non-citrate)
Base excess (mmol/l)	-7.7/-6.9	-3.7/-6.8*	-4.4/-4.1
Sodium concentration (mmol/l)	137.0/136.7	135.9/136.3	137.0/137.1
Potassium concentration (mmol/l)	4.2/4.3	4.5/4.6	4.3/4.5

*p<0.001, two sample *t* test.

of acidosis, there was no obvious advantage of the citrate containing hypotonic ORS over the composition without citrate. The rehydration properties of the two solutions appeared to be equal.

Previous studies in the diseased rat model and in healthy human volunteers have indicated that a base or base precursor may have only a minor role in the absorption of an ORS. Lifshitz and Wapnir found that in the rat small intestine the addition of up to 30 mmol/l of bicarbonate in an ORS did not increase and 40 mmol/l of bicarbonate actually reduced the net absorption of water³; similar results were found when bicarbonate was replaced by citrate. Rolston *et al* showed that bicarbonate and acetate can increase absorption in healthy rat small intestine,¹² and acetate and citrate in healthy human jejunum.¹⁷ Elliot *et al* found similar results.¹³ Both study groups showed, however, that in a secretory rat intestine (induced by cholera toxin) the inclusion of bicarbonate significantly reduced the water absorption compared with bicarbonate free solution.^{12 13}

It is remarkable that although in our study the patients receiving ORS without citrate consumed significantly more ORS, the duration of diarrhoea was not longer than in those receiving the ORS with citrate. This suggests that the absorption properties of a hypotonic ORS without citrate were good, and the solution did not induce osmotic diarrhoea. This might be due to the low glucose concentration of 64 mmol/l, resulting in a sodium:glucose ratio of 1:1.

Our study has shown that a hypotonic ORS with osmolality of 224 mmol/l is effective for the correction of diarrhoeal dehydration even without a base precursor. A citrate-containing solution will correct metabolic acidosis earlier, however, and therefore citrate is recommended for the composition of a hypotonic ORS. If, for example, in developing countries, the manufacture, packaging or storage of an ORS with a base precursor is difficult, a hypotonic ORS without a base precursor might be considered as an option. For home made salt-sugar solutions in particular a hypotonic formula

without citrate might be advantageous, and should, in the future, be directly compared with the isotonic sugar-salt solutions recommended at present.

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