Citrate can effectively replace bicarbonate in oral rehydration salts for cholera and infantile diarrhoea

M. R. Islam¹

The therapeutic effectiveness of oral rehydration salt (ORS) solutions containing trisodium citrate (ORS-citrate) in place of sodium bicarbonate (ORS-bicarbonate) was evaluated in a double-blind, randomized clinical trial on 74 children with cholera and 34 infants and young children ( < 2 years) with infantile diarrhoea. All patients had moderate-to-severe dehydration. Patients with severe dehydration were initially rehydrated with intravenous fluid followed by maintenance therapy with ORS solution (either ORS-bicarbonate or ORS-citrate). Children who had moderate dehydration received either ORS-bicarbonate or ORS-citrate solution during both the initial and the maintenance phase of therapy. The results of the study suggest that ORS-citrate, which has the advantage of a longer shelf-life in hot and humid climates, can safely and effectively be used instead of ORS-bicarbonate for hydration and correction of acidosis in cases of cholera and infantile diarrhoea.

The introduction of oral rehydration salts (ORS) has been a major advance in modern medicine. Use of an ORS solution with a sodium bicarbonate concentration of 30 mmol/l has been recommended by WHO for treatment of acute diarrhoea in patients, irrespective of age. Bicarbonate ions are directly absorbed from the gut and counteract acidosis. Although ORS solutions containing sodium bicarbonate are very effective in this respect, they have some practical disadvantages. For example, when the constituents are mixed together as solids in polyethylene packets in tropical climates, sodium bicarbonate reacts with glucose or sucrose to form brown polymers of 5-hydroxymethylfururaldehyde (J).

Trisodium citrate dihydrate is a stable salt and, in contrast to sodium bicarbonate, does not react so readily with glucose or sucrose. Animal experiments have shown that citrate is actively absorbed by rabbit ileum via an ouabain-sensitive, chloride-independent mechanism that also stimulates active absorption of sodium and chloride ions (2). Clinical studies have also shown that trisodium citrate dihydrate can effectively replace sodium bicarbonate wholly or partly in ORS for rehydration and correction of acidosis in adults and children with diarrhoea (3–5). We therefore tested the efficacy of trisodium citrate dihydrate in ORS solutions for the management of cholera and infantile diarrhoea and describe our results here.

MATERIALS AND METHODS

The study was carried out at the International Centre for Diarrhoeal Disease Research, Bangladesh, from August 1983 to January 1984. One hundred and eight children of less than 12 years of age who presented with a history of severe, watery diarrhoea of < 96 hours’ duration and who were considered clinically to have either severe or moderate dehydration, but who had not been rehydrated intravenously, participated in the study. The degree of dehydration was assessed according to WHO guidelines. Stool specimens obtained on arrival at the centre were rapidly screened for Vibrio cholerae by darkfield microscopy (6). Darkfield-positive children and darkfield-negative infants and children < 2 years of age were selected. Patients who had taken medications during the week prior to admission or who presented with other complications not related to dehydration were excluded from the study. After parental consent had been obtained and brief clinical histories and physical examinations undertaken, the children were assigned using a random number table to treatment with either ORS solution containing sodium bicarbonate (ORS-bicarbonate solution) or an ORS solution containing trisodium citrate dihydrate (ORS-citrate solution).

¹ Associate Scientist, International Centre for Diarrhoeal Disease Research, Bangladesh, G.P.O. Box 128, Dhaka-2, Bangladesh. Requests for reprints should be sent to Dr G. H. Rabbani at this address.
Table 1. Composition of oral rehydration salt (ORS) solutions

<table>
<thead>
<tr>
<th>Constituent</th>
<th>ORS-citrate</th>
<th>ORS-bicarbonate</th>
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<tbody>
<tr>
<td>Sodium chloride</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Trisodium citrate dihydrate</td>
<td>2.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Glucose, anhydrous</td>
<td>20.0</td>
<td>20.0</td>
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</table>

instead of the bicarbonate. The compositions of the two solutions are shown in Table 1.

Laboratory technicians prepared packets of both types of ORS salts, verified their chemical composition, and coded them for the double-blind test. Nursing staff dissolved the contents of the packets according to a random schedule before administering the solutions to the patients. Each patient was placed in a cholera cot provided with a plastic sheet designed to collect liquid stool. Those patients with severe dehydration (undetectable or low-volume radial pulse and poor mentation) were rehydrated by infusion with intravenous normal saline solution (100 ml/kg body weight) within 4 hours of admission. Children who were only moderately dehydrated received within 4 hours either ORS-citrate or ORS-bicarbonate solution (100 ml/kg body weight) for initial rehydration therapy. To maintain hydration, all children were encouraged to drink ORS solution in volumes that equalized their purging until diarrhoea stopped.

Patients who failed to rehydrate or maintain hydration on ORS solution alone were considered oral therapy failures and were removed from the study. These children were then rehydrated intravenously. The criteria for failure of treatment were based on clinical assessment, the results of intake and output balance, and failure to gain body weight. Consumption of breast milk and/or half-strength cow’s milk was allowed from 4 hours after admission. The amount of milk ingested was determined by weighing the child before and after each feed. Older children able to take solid food received the regular Bengali diet of rice and curry.

Patients were monitored continuously by a doctor and by experienced nurses, and the clinical signs of hydration status were recorded along with intake and output measurements at 8-hour intervals. Patients remained in the hospital until no watery or liquid stool was passed for 16 hours or until formed stool was passed.

Blood samples for determination of haematocrit (erythrocyte volume fraction), plasma specific gravity, and concentration of electrolytes were taken before and after 24 hours of therapy and when diarrhoea had stopped. The concentrations of serum Na⁺ and K⁺ were determined using a flame photometer, the concentration of bicarbonate using an auto-analyser, and the plasma specific gravity using a refractometer. Stool samples were collected and cultured for salmonella spp., shigella spp., and Vibrio cholerae. Tests for heat-labile (7) and heat-stable (8) enterotoxins of Escherichia coli and an ELISA test (9) for rotavirus were only carried out with children younger than 2 years of age who had infantile diarrhoea. Children aged less than 8 years who had cholera received furazolidone (5 mg/kg/day), while those older than 8 years received tetracycline (1 g/day in 4 equally divided doses) for 3 days; however, children with infantile diarrhoea received no antibacterial chemotherapy.

The effectiveness of treatment was assessed by comparing the success rates, stool output, ORS intake, gain in body weight, changes in erythrocyte volume fraction and plasma specific gravity, correction of acidosis, and maintenance of electrolyte balance at 24 hours after commencement of therapy and when diarrhoea had stopped for children receiving either ORS-bicarbonate or ORS-citrate. Data were analysed by the χ² test and by a two-tailed normal test (2-test). Nine children (3 in the ORS-citrate and 6 in the ORS-bicarbonate group) who failed to rehydrate on ORS solutions were excluded from the analysis but data from these children are included in Table 2.

RESULTS

The clinical characteristics of the two groups of children with cholera and infantile diarrhoea are shown in Table 2. Both groups had comparable epidemiological, clinical, biochemical, and diagnostic features on admission. More than half of the children with cholera had severe dehydration and acidosis. Of children with cholera, 92% of those who received ORS-citrate and 86% of those who received ORS-bicarbonate were successfully treated. This compares with a success rate of 100% for young children with infantile diarrhoea who received ORS-citrate and 94% for those who received ORS-bicarbonate.

The nine treatment failures (3 in the ORS-citrate group and 6 in the ORS-bicarbonate group) were withdrawn from the study because of persistent vomiting and severe diarrhoea (greater than 250 ml/kg/day). These children were subsequently treated
<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Duration of diarrhoea before admission (hours)</th>
<th>Body weight (kg)</th>
<th>Clinical dehydration (%)</th>
<th>Acidosis (%)</th>
<th>Haematocrit (%)</th>
<th>Plasma specific gravity</th>
<th>Serum concentration (mmol/l) of Na⁺</th>
<th>K⁺</th>
<th>HCO₃⁻</th>
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<tbody>
<tr>
<td><strong>Cholera</strong></td>
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<tr>
<td>ORS-citrate (&lt;i&gt;n = 39&lt;/i&gt;)</td>
<td>5.0 ± 2.5</td>
<td>11.3 ± 5.3</td>
<td>11.8 ± 3.9</td>
<td>42</td>
<td>58</td>
<td>76</td>
<td>44.8 ± 6.9</td>
<td>1.033 ± 0.004</td>
<td>135 ± 5.1</td>
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<tr>
<td>ORS-bicarbonate (&lt;i&gt;n = 35&lt;/i&gt;)</td>
<td>4.6 ± 2.5</td>
<td>16.4 ± 15.6</td>
<td>10.6 ± 3.6</td>
<td>34</td>
<td>66</td>
<td>74</td>
<td>45.6 ± 6.0</td>
<td>1.033 ± 0.004</td>
<td>134.5 ± 3.5</td>
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<tr>
<td><strong>Infantile diarrhoea</strong></td>
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<tr>
<td>ORS-citrate (&lt;i&gt;n = 17&lt;/i&gt;)</td>
<td>1.0 ± 0.5</td>
<td>46.9 ± 46.1</td>
<td>6.3 ± 1.3</td>
<td>100</td>
<td>0</td>
<td>65</td>
<td>33.7 ± 4.2</td>
<td>1.026 ± 0.002</td>
<td>138.2 ± 5.5</td>
</tr>
<tr>
<td>ORS-bicarbonate (&lt;i&gt;n = 17&lt;/i&gt;)</td>
<td>0.9 ± 0.5</td>
<td>30.7 ± 26.0</td>
<td>6.4 ± 1.0</td>
<td>88</td>
<td>12</td>
<td>70</td>
<td>36.2 ± 4.2</td>
<td>1.027 ± 0.002</td>
<td>139.0 ± 4.5</td>
</tr>
</tbody>
</table>

* Taken to be a bicarbonate concentration ≤ 16 mmol/l.
intravenously. Children with severe cholera were more likely to fall on oral maintenance therapy. These children could be identified by the following three criteria: (1) undetectable radial pulse on admission; (2) plasma specific gravity > 1.034; (3) initial 24-hour high purging rate (> 250 ml/kg/day). Although the majority of children vomited during the first 24 hours after admission, the amount of fluid lost in this way was relatively small in comparison to stool output.

The results obtained indicate that treatment with ORS-citrate is as successful as that with ORS-bicarbonate in terms of its ability to rehydrate, correct the acidosis, and maintain the concentrations of serum Na⁺, K⁺, and other electrolytes, both 24 hours after commencement of therapy and when diarrhoea had stopped (Table 3).

More than 60% of the children with cholera who required emergency intravenous fluid replacement therapy were severely dehydrated. In contrast, severe dehydration was less frequent in infants with non-choleraic diarrhoea, who seldom required emergency intravenous rehydration.

The majority of cholera patients who received ORS-citrate (87%) or ORS-bicarbonate (88%) were of classical Ogawa serotype. For infantile diarrhoea the etiologic agents identified were enterotoxigenic E. coli (18%) and rotavirus (8%) in young children treated with ORS-citrate, and enterotoxigenic E. coli (23%) and rotavirus (25%) in those treated with ORS-bicarbonate.

**DISCUSSION**

The results of the study demonstrate that ORS-citrate solution is as effective as ORS-bicarbonate solution for rehydration and correction of acidosis in cases of paediatric cholera and infantile diarrhoea. A success rate of greater than 90% for oral therapy with ORS-citrate for both children with cholera and infantile diarrhoea compares well with the success rates with ORS-bicarbonate and is much higher than the rates reported in other studies (3, 10, 11). This is mainly because in the present study severe cases of dehydration were initially rehydrated intravenously.
ORAL REHYDRATION SALTS WITH CITRATE

We have previously reported the results of attempts to rehydrate with ORS solutions alone all diarrhoea patients, including cholera patients with moderate to severe dehydration caused by heavy purging and persistent vomiting, who normally would have needed initial intravenous fluid therapy (3). The results of the present study corroborate our previous proposal that if intravenous fluid is used only for initial rehydration of patients suffering from severe or moderate-to-severe dehydration, oral failure rates can be reduced considerably. In our previous study (3) we did not use antibiotics, even for cases of cholera, but in the present study we used furazolidone or tetracycline and this also contributed significantly to the ORS success rate by decreasing the purging rate as early as 6 hours after administration of the drug (12).

The results of the study reported here suggest that trisodium citrate dihydrate can effectively replace sodium bicarbonate in the standard ORS solution for treatment of children with severe cholera if used as an adjunct to standard hydration and antibiotic therapy. Infantile diarrhoea associated with less severe dehydration can also be treated successfully without additional intravenous fluid and antibiotic therapy. The group of children most likely to fail with ORS therapy are those admitted in a state of shock and with a purging rate of > 250 mL/kg/day. Generally such children have plasma of high specific gravity (> 1.034) on admission.

The study also indicates that the trend among children who received ORS-citrate solution was towards a lower mean purging rate, lower ORS intake, and less vomiting; however, this was not statistically significant. This suggests that ORS-citrate solution is well absorbed and tolerated. Considerable improvement in ORS may be feasible when trisodium citrate dihydrate is used in conjunction with other absorption-promoting agents (3, 4) that can replace the deficit of water and electrolytes more efficiently than the ORS formulation recommended by WHO.

ACKNOWLEDGEMENTS

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RÉSUMÉ

L'efficacité thérapeutique d'une solution de sels de rehydratation orale (SRO) contenant du citrate trisodique (SRO avec citrate) au lieu de bicarbonate de sodium (SRO avec bicarbonate) a fait l'objet d'un essai clinique prospectif randomisé, en double insu, visant à apprécier son pouvoir de réhydrater les malades et à corriger l'acidose associée au choléra et à la diarrhée infantile. L'étude a porté sur 74 enfants âgés de moins de 12 ans atteints de choléra et sur 34 nourrissons et jeunes enfants (de moins de 2 ans) atteints de diarrhée, qui présentaient une déshydratation et une acidose modérées ou graves au moment de l'hospitalisation. Ces enfants ont été traités soit au moyen de SRO contenant 2,5 g de bicarbonate de sodium, soit au moyen de SRO contenant 2,9 g de citrate trisodique, à deux molécules d'eau, par litre de solution. Les autres composants des SRO étaient les mêmes dans les deux solutions. On a administré par voie intraveineuse une solution saline normale (100 mL/kg de poids corporel) aux patients atteints de choc hypovolémique pour corriger la déshydratation initiale, alors que les malades modérément déshydratés ont reçu une solution de SRO avec bicarbonate ou de SRO avec citrate (100 mL/kg de poids corporel). L'apport de SRO, le volume des selles émises et la fréquence des vomissements ont été déterminés toutes les huit heures. Pour doser le volume globulaire (hématocrite), la densité plasmatique et les concentrations d'électrolytes, on a effectué des prélèvements de sang au moment de l'hospitalisation, 24 heures après le début du traitement et à la fin de l'épisode diarrhéique. On a recueilli chez chaque enfant un échantillon des selles pour la culture de Vibrio cholerae, Salmonella spp. et Shigella spp. On a recherché, chez les seuls nourrissons et jeunes enfants atteints de diarrhée, les Escherichia coli producteurs d'enterotoxines thermolабiles et thermostables, ainsi que le rotavirus par la méthode ELISA. On a apprécié l'efficacité des deux solutions de SRO en comparant le taux de succès global de la thérapeutique orale, le volume des selles émises,
l'apport de la solution de SRO, la prise de poids, l'abaissement de l'hématocrite et de la densité plasmatique, la correction de l'acidose et le maintien de l'équilibre électrolytique après 24 heures de traitement et lorsque la diarrhée a cessé.

Quatre-vingt douze pour cent des enfants atteints de choléra qui ont reçu une solution SRO avec citrate et 86% de ceux qui ont reçu une solution SRO avec bicarbonate ainsi que tous les nourrissons et jeunes enfants, à l'exception d'un cas (appartenant au groupe SRO avec bicarbonate), ont été traités avec succès. Les neuf échecs thérapeutiques (3 dans le groupe SRO avec citrate et 6 dans le groupe SRO avec bicarbonate) ont été retirés de l'étude en raison de vomissements persistants et du volume élevé des selles émises (supérieur à 250 ml/kg/jour). Chez les cholériques traités avec succès au moyen d'une solution de SRO avec citrate, la concentration sémique moyenne de HCO₃⁻ est passée de 13,7 mmol au moment de l'hospitalisation à 18,4 et 23,0 mmol, respectivement, après 24 heures de traitement et à la fin de l'épisode diarrhéique. En ce qui concerne les malades qui ont reçu la solution de SRO avec bicarbonate recommandée par l'OMS, la concentration de HCO₃⁻ est passée de 14,4 mmol/l à 17,8 et 22,9 mmol/litre, respectivement. Les deux solutions de SRO ont corrigé l'acidose chez les nourrissons et jeunes enfants atteints de diarrhée. Il n'a été observé aucune différence significative dans les concentrations sémiques de Na⁺, K⁺ et HCO₃⁻ entre les sujets ayant bénéficié de l'un ou l'autre des traitements.

D'après les résultats de cette étude le citrate trisodique, à deux molécules d'eau, dont la durée de conservation est supérieure à 0,5 des climats tropicaux, peut efficacement remplacer le bicarbonate de sodium dans les solutions de SRO destinées au traitement du choléra et de la diarrhée infantile.

REFERENCES


