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# RESEARCH ON ORAL REHYDRATION THERAPY FOR DIARRHOEAL DEHYDRATION

by

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## 1. Introduction

Although oral rehydration therapy had been used for a number of decades, it did not begin to gain global acceptance as an effective, practical weapon for the treatment of diarrhoeal dehydration until the mid-1960's, when Phillips and coworkers demonstrated in careful balance studies that glucose, sodium, potassium, bicarbonate and water could be absorbed in patients with acute diarrhoea. These observations were soon confirmed and extended in controlled balance studies in Pakistani and Indian adults and children with cholera, which showed that oral therapy could reduce intravenous fluid needs by 80% in patients in shock and could be used without any intravenous fluid to treat patients with mild or moderate dehydration. These latter studies also demonstrated that,with combined use of intravenous and oral therapy,mortality in hospitalized patients presenting with shock could be reduced to under 1%. Many subsequent studies have now demonstrated the efficacy of oral glucose-electrolyte therapy in non-cholera diarrhoeas in all age groups. This paper will summarize the results of research that has been conducted in oral rehydration therapy, and suggest priority areas for future study.

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## 2. Composition of oral solution

The ingredients and composition of the oral fluid (ORS) which has been widely and effectively used, and which is recommended by the World Health Organization, are shown in the table below:

Table. INGREDIENTS AND COMPOSITION OF WHO RECOMMENDED ORAL REHYDRATION SOLUTION (ORS)

| Ingredient | Grams/litre water |
|---|---|
| Sodium chloride | 3.5 |
| Sodium bicarbonate | 2.5 |
| Potassium chloride | 1.5 |
| Glucose | 20 |

| Composition | mmol/litre of water |
|---|---|
| Sodium | 90 |
| Potassium | 20 |
| Chloride | 80 |
| Bicarbonate | 30 |
| Glucose | 111 |

The composition of oral fluid was initially based on studies of the electrolyte concentration of stools of cholera patients by Phillips and coworkers who demonstrated that rehydration solutions should replace all water and electrolyte losses simultaneously and that absorption of orally administered sodium occurred only in the presence of glucose. Several studies in Dacca and Calcutta, cited above, confirmed these findings and showed that absorption of oral solutions occurred, without a significant increase in diarrhoea, at a glucose concentration of 2% but not at significantly lower concentrations.

The sodium concentration of stools from severely purging adults with cholera was found to average 120-130 mmol/l, and oral therapy with glucose-electrolyte solutions containing 120 mmol/l of sodium were used successfully in the treatment of these patients. Subsequent studies showed that a solution with 90 mmol/l of sodium could also be used (provided that adult cholera patients received up to 1.5 times the volume of their stool losses) and that such a solution had the advantage of better meeting the needs of children with cholera and also of patients of all ages with non-cholera diarrhoea whose stool sodium concentration is lower.

Following the demonstration that absorption of oral bicarbonate and potassium remained intact during diarrhoea without glucose, several workers showed that acidosis could be corrected using oral fluid containing 30-48 mmol/l of bicarbonate An oral solution containing 20 mmol/l of potassium has been found adequate for replacement of stool potassium losses in adults and children, although, as discussed later, additional potassium intake may be advantageous for infants.

3. Experience with oral therapy

Since the early studies in Bangladesh and India oral rehydration has gained worldwide acceptance. One of the earliest and most dramatic demonstrations of its efficacy and benefit was its use, under the most difficult field conditions, in the maintenance of hydration in severely dehydrated Bangladesh refugees during the 1971 civil upheaval.

Many Asian and African countries experiencing cholera during the present pandemic have used oral rehydration therapy with remarkable success; one recent example was in the outbreak of cholera in the Maldive Islands in 1977. A number of countries, including Indonesia, Pakistan and Costa Rica, have documented a reduction in diarrhoea-related mortality and/or amount of intravenous fluid used after oral rehydration therapy was introduced into treatment facilities. The Infectious Diseases Hospital in Calcutta claims to have saved 70% of the expenses previously incurred for intravenous fluid by the judicious use of oral fluid. Approximately 50 other countries are presently using oral rehydration therapy in their treatment facilities for all dehydrating diarrhoeas, many after acquiring experience in the treatment of cholera.

4. Infantile diarrhoea

Recently there have been a number of studies of the use of oral rehydration therapy in the treatment of infantile non-cholera diarrhoeas. One of the first, conducted in American Indians, demonstrated that most infants with mild dehydration could be treated by oral rehydration alone with a corresponding reduction in the use of intravenous fluids. A subsequent study in Calcutta demonstrated that oral rehydration was highly effective in the treatment of more severely dehydrated infants who received ORS with additional plain water or a solution with a lower sodium concentration (50 mmol/l). The efficacy of oral rehydration fluid in infants was confirmed by a later study in Goa, India. In a more recent study in Costa Rica, 94% of infants with moderate to severe dehydration were safely rehydrated with ORS given with extra plain water in the ratio of two parts ORS followed by one part of water. The results were the same in malnourished and eutrophic infants. Although 63% of infants vomited, only 4% required intravenous fluids, confirming information from many previous studies conducted in adults and older children that vomiting during therapy is usually not an obstacle to successful use of oral rehydration therapy.

A study just completed in Jamaica has compared the safety and efficacy of ORS given without plain water and a solution with 60 mmol/l of sodium in the treatment of infants with moderate to severe dehydration. The ORS used alone was found to be safe, although a few cases had transient serum sodium elevations without associated clinical findings. A significant number of those receiving the 60 mmol/l solution had persistently low serum sodium. More significantly, only one of 84 infants in the 2 groups combined required intravenous therapy.

A further Costa Rican study also just completed has conclusively demonstrated the safety of oral rehydration in neonates. In this study 39 of 40 dehydrated neonates were successfully rehydrated and maintained in water and electrolyte balance using ORS administered with plain water in a fixed ratio as described above in the previous Costa Rican study. Only one neonate required intravenous fluid.

Data from the studies on infantile diarrhoea have shown that infants lose more potassium in their stools than adults. In a second Jamaican study it was found that 17% of infants with moderate to severe dehydration who received ORS (potassium concentration 20 mmol/l) had persistent hypokalemia although none had associated clinical findings. In contrast, in a group receiving a solution containing 35 mmol/l there was greater net positive potassium balance and no hypokalemia. Since potassium depletion may be associated with anorexia and other abnormalities, it appears that a higher potassium concentration in the ORS may offer a potential advantage for infants.

In a recent WHO consultation[1] it was concluded, based on these and other studies, that the WHO recommended ORS which is highly suitable for use in older children and adults is also safe and effective in infants provided that extra plain water is administered and specific guidelines are followed in therapy such as those used in the Costa Rican studies.

5. Glucose versus sucrose

Because of the high cost or non-availability of glucose in some countries and the desire to produce packages of the oral rehydration salts locally, a number of studies have been undertaken to determine whether sucrose can be substituted for glucose in the formulation. In a small initial study carried out in Bangladesh a sucrose-electrolyte solution was successfully employed in maintenance therapy of adult patients presenting with severe dehydration. Subsequent controlled trials in Costa Rica, Bangladesh and Calcutta have shown that in cholera and non-cholera diarrhoeas in all age groups sucrose can be substituted for glucose in the oral fluid, although the use of sucrose is associated with more vomiting and with slightly lower success rates, especially in patients with profuse diarrhoea. In all these studies, in order to obtain the same osmolarity as glucose, the sucrose concentration in grams per litre has been twice that of glucose. One can conclude from the available information that from a physiological standpoint glucose and sucrose are both effective, but when both are available, glucose is to be preferred. Because it has been possible in many of these studies to determine the etiological agents responsible for many of the cases, these studies have also demonstrated that oral rehydration therapy can be used successfully in acute watery diarrhoeas of divers etiologies, including those caused by rotavirus and common bacterial pathogens.

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1 Finberg, L., Mahalanabis, D., & Nalin, D., Oral Therapy for Dehydration in Acute Diarrhoeal Diseases with special reference to the Global Diarrhoeal Diseases Control Programme - Unpublished document BAC/DDC/79.1

## 6. Delivery of oral rehydration at the periphery

Attention is increasingly being focussed on extending the delivery of oral therapy to the village and household levels where it would have a greater impact on associated mortality. Therapy at these levels, if properly applied early in the course of illness, may be expected to prevent the development of severe dehydration and the need for intravenous therapy and hospital referral. Delivery of oral rehydration therapy at the periphery will continue to need adequate referral or backup facilities, with access to intravenous therapy. Data derived from clinical observations of severe cholera in volunteers as well as in patients with rotavirus diarrhoea have shown that severe vomiting may sometimes occur early in the course of these illnesses, making oral rehydration therapy difficult.

Controlled field evaluations of the effectiveness of early oral rehydration therapy are not easy to carry out. The first such trials were undertaken in the Philippines, and later in Turkey, where ORS was delivered by nurse midwives in health centres or health posts after a brief training period. These studies demonstrated the feasibility, acceptability and effectiveness of the procedure but were unable to demonstrate a reduction in referrals because of the small size of the study populations. In a recent study in Bangladesh home delivery of oral rehydration solution by village health workers, with instructions to mothers, reduced the numbers of cases seeking therapy at a rural treatment centre by 29%; this study was limited to a 4-month period and was carried out in a setting where the workers were providing only diarrhoea treatment. Other evaluations are needed, especially in populations served by multi-purpose village health workers; such studies are under way in Bangladesh and Costa Rica.

Other examples of oral rehydration being given successfully at home by mothers have been the studies conducted in Costa Rica and Jamaica. In both these studies aides successfully instructed and enlisted the help of mothers in the oral rehydration of their acutely ill infants presenting with moderate dehydration to an emergency room where previously only intravenous therapy had been used.

Mothers were then taught how to mix and administer ORS at home and how to assess skin elasticity. In the Costa Rica study, after initial rehydration in the emergency room 87 of 100 infants were satisfactorily managed at home by their mothers; of the 13 infants brought back to the emergency room during their illness, only six were found to need intravenous fluids and the rest recovered with small amounts of additional oral therapy.

Because diarrhoea in its earliest stages is not usually associated with acidosis, a number of health personnel have advocated that educational programmes be instituted instructing mothers to give their children a solution made from household salt and sugar early in the course of diarrhoea; such solutions would presumably diminish the number of cases requiring further treatment by village health workers. Many recommendations currently exist regarding the use of "special measuring spoons", domestic spoons, and "pinch and scoop" methods for preparing such solutions. A few trials done to date have shown that domestic ingredients vary widely in purity and that solutions prepared by mothers using any of these methods differ considerably in salt concentrations, many of them tending to be unacceptably high.

The results of a recently completed study in Bangladesh have demonstrated that mild to moderately dehydrated cases of non-cholera diarrhoea can be rehydrated with this "incomplete" formula solution, although the period of acidosis is significantly prolonged. In a field programme carried out in Punjab, India, a salt-sugar solution was used by village health workers for the treatment of diarrhoea and was reported to have led to a decrease in mortality; however, this study was conducted over a brief period and it was not clear whether the decrease in mortality was due to the oral rehydration programme or to normal seasonal and yearly fluctuations in mortality. Other studies of the efficacy of these solutions when used at home by mothers are soon to be instituted or are under way and will provide information on the utility and efficacy of this approach.

7. Nutritional benefit

Field trials conducted in the Philippines and Turkey,mentioned earlier, showed that infants and young children who received ORS, along with proper dietary management using locally available foods, for the treatment of acute diarrhoea

gained more weight during the period of observation than those not receiving ORS. Subsequent similarly designed studies in Liberia, Iran and Egypt have shown a similar trend in weight gain. This increase in weight may have been due to more rapid restoration of appetite in those children receiving the oral rehydration fluid because of the earlier correction of electrolyte imbalance. Such studies indicate that oral rehydration therapy may have an important nutritional benefit and emphasize the need for the complete rehydration formula and proper education of the mothers.

8. Other pharmaceutical agents

Many clinical studies have revealed that antibiotics and other drugs have only a very limited role in the therapy of acute diarrhoeas. Antibiotics should be used only in certain specific bacterial diarrhoeas, particularly cholera and severe Shigella dysentery, as well as in diarrhoeas caused by Giardia and Entamoeba histolytica (the latter two diseases rarely present as acute watery diarrhoea or cause dehydration). Many of the commonly used antidiarrhoeal medications (e.g., kaolin, pectin, bismuth, Lomotil*, paregoric) have not been shown to be useful in the treatment of acute diarrhoea and Lomotil and paregoric may be harmful when used in children.

9. Current research needs

Additional research is needed in a number of areas:

- To investigate the accuracy of salt and sugar solutions made at home and of their impact in reducing referrals, hospitalization and mortality from diarrhoeal diseases when used early in the course of illness;
- To determine the most suitable methods of administering oral rehydration solutions with the WHO recommended formulation (90 mmol/l sodium) to infants;
- To evaluate the advantages of using oral solution containing a higher potassium concentration (e.g., 25 mmol/l) in all age groups.
- To determine the benefit of adding to the oral rehydration solution certain amino acids, including glycine, which may enhance the intestinal salt and water absorption and thus reduce stool output by a mechanism distinct from that of glucose-mediated absorption. Two studies have demonstrated that the addition of glycine to the oral solutions results in greater fluid absorption and a significant reduction in the duration and volume of diarrhoea in adults and children with cholera and non-cholera diarrhoeas.

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* Diphenoxyl hydrochloride with atropine

- To confirm the nutritional benefit of oral rehydration therapy and to identify the mechanisms of this effect;
- To evaluate antisecretory agents, such as chlorpromazine and nicotinic acid, and of anti-emetics to determine whether these agents have an adjunctive role in diarrhoea therapy.

10. Conclusions

Research on intestinal absorption and stool composition has led to the "rediscovery" of oral therapy and has given it a strong scientific basis. The results of balance studies and of studies with different therapeutic regimens have helped to establish practical methods for the administration of these solutions in hospitals and other treatment facilities with, as a result, a markedly reduced dependence on intravenous fluids. Further benefits can be expected from carefully planned national training, health education and information dissemination programmes which take into account cultural variations and other local factors. Proper evaluation including determination of optimal benefit-risk ratios is necessary for the development of appropriate methods for delivery of oral rehydration to the periphery.