



DIARRHOEAL DISEASES CONTROL PROGRAMME

CLINICAL MANAGEMENT OF ACUTE DIARRHOEA

Report of a Scientific Working Group
(New Delhi, 30 October - 2 November 1978)

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R 1179 - 680

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1. INTRODUCTION

A Scientific Working Group on Oral Rehydration Therapy met at the WHO Regional Office for South-East Asia, New Delhi, from 30 October to 2 November 1978.

It was with particular satisfaction that the Regional Office had agreed to host the meeting as the South-East Asia Region had a long-standing interest in and commitment to the control and treatment of diarrhoeal diseases, and was the Region in which oral rehydration therapy had originally been developed. Six of the ten countries in the Region were already using oral rehydration therapy for the treatment of diarrhoeas.

The Group was informed of the current status of the new Diarrhoeal Diseases Control (DDC) Programme of the World Health Organization, which is a technical cooperation activity with Member States being developed in partnership with UNICEF. Oral Rehydration therapy was a strategy that had been given high priority in the Programme and the Scientific Working Group had been established primarily to provide the Organization with the necessary guidance for its development and implementation as part of country health programmes. The objectives of the meeting, therefore, were: to review current knowledge on oral rehydration therapy and other aspects of the clinical management of diarrhoea including the use of drugs; to establish priorities for further research in these areas; to recommend an approach for global implementation of national DDC programmes which emphasize oral rehydration therapy; and to define training needs for these programmes.

2. REVIEW OF CURRENT KNOWLEDGE

Considerable hospital and field experience has been gained during the last decade in the use of a glucose-electrolyte oral rehydration solution as a simple treatment for dehydration in acute diarrhoeal diseases. This has been due in large part to the promotional activities of the World Health Organization. The WHO Advisory Group on Development of a Programme for Diarrhoeal Diseases Control that met in May 1978¹ reviewed the various possible strategies for this Programme and their applicability under the prevailing circumstances. They concluded that the strategy that can be applied now with available means and which will have the greatest immediate impact on a global basis is wide implementation of oral rehydration therapy.

The concept of giving diarrhoea patients liquids varying from plain water to complex proprietary products by mouth is not new; what is new is the development of a simple single mixture which can treat and prevent dehydration caused by diarrhoea of any etiology in all age groups. The composition of this mixture is based on knowledge gained from research on intestinal absorption and secretion. Although the mixture provides a source of calories, it is primarily intended to restore normal fluid and electrolyte balance and not to provide caloric or other nutritional needs.

Some public health workers in the developing countries, realizing the immediate benefits of oral rehydration and faced with difficulties in making it available where it is needed most, have tried to simplify the composition of the mixture or its means of delivery; these efforts have not yet been fully evaluated. On the other hand, some paediatricians, particularly in countries with temperate climates, are concerned that the sodium concentration in the recommended composition may be rather high for use in young infants. Because of these and other questions that have been raised, the Group felt it necessary to review the available information on the risks and benefits of the recommended composition of the fluid in the light of the possible delivery systems for wide implementation of oral rehydration therapy, and to consider other aspects of the clinical management of acute diarrhoea, especially the use of drugs and dietary management.

2.1 Oral rehydration therapy

2.1.1 Composition of oral rehydration fluid

The basic ingredients of oral rehydration fluid are water, sodium chloride, sodium bicarbonate, potassium chloride and glucose or a substrate such as sucrose that can be degraded into glucose in the small intestine. The choice of ingredients and their concentrations have been based on known fluid and electrolyte losses during diarrhoea and on balance studies conducted mostly in cholera patients which demonstrated that glucose-mediated sodium absorption is intact during illness and helped to determine the concentrations of the ingredients which result in their optimum absorption. Satisfactory oral fluid intake allows absorption rates to exceed water and electrolyte losses in diarrhoea and vomitus without an increase in diarrhoea losses. Physiological adjustments of small excesses or deficits of water and electrolytes are made by the kidneys, lungs and sweat glands.

Since 1971 WHO has been recommending the following composition of oral rehydration fluid:

<u>Ingredient</u>	<u>grams/litre water</u>
Sodium chloride	3.5
Potassium chloride	1.5
Sodium bicarbonate	2.5
Glucose	20.0

The composition results in the following concentrations:

	<u>mmol/litre</u>
Sodium	90
Potassium	20
Chloride	80
Bicarbonate	30
Glucose	111

Information about the ingredients of the fluid, much of which led to and continues to support this composition, is summarized below.

Water: Any safe drinking water can be used. When available water is of doubtful quality, it should be boiled and cooled beforehand or purified by other means available. Microbiological studies have shown that Escherichia coli, Vibrio cholerae, Salmonella and Shigella do not multiply in oral rehydration fluid and survive in declining numbers for up to 48 hours.

Sodium: Studies in patients with acute cholera demonstrated that sodium and water given by mouth are poorly absorbed in the small intestine in the absence of glucose. Clinical studies have been carried out using glucose-containing solutions with sodium concentrations up to 180 mmol/litre. Those solutions lacking any sodium led rapidly to a marked negative sodium balance during high-output diarrhoea. Solutions with 180 mmol/litre of sodium caused excess absorption, hypernatraemia, overhydration and cardiopulmonary failure. A number of studies have shown solutions with a sodium concentration in the range of 90 to 120 mmol/litre to be safe and effective for the therapy of cholera and severe non-cholera diarrhoeas in adults and older children.^{2,3} In infants and young children, mostly with non-cholera diarrhoea, solutions containing 50 to 90 mmol/litre of sodium have been safely used although the amount of free water and food given in these studies has varied.⁴⁻⁷

A single solution containing 90 mmol/litre of sodium is generally considered to be the most practical for the following reasons: (1) in general, for all causes of diarrhoea, the sodium concentration of the fluid for rehydration (replacement of initial losses) needs to be close to the plasma concentration to be effective; (2) for the treatment of cholera, which is endemic in many countries in Asia and Africa, a fluid with a relatively high sodium concentration is required^{*}; (3) although some acute diarrhoeas in infants and young children can be treated with a fluid containing a lower sodium concentration, these cases often cannot be clinically distinguished from cholera which, although uncommon, occurs in this age group; (4) use of a formula with a sodium concentration of 90 mmol/litre has been found effective in millions of children and adults and in many countries for the treatment of cholera and non-cholera diarrhoea and side effects have been extremely rare, even in young children; transient peri-orbital oedema has occasionally been observed in infants, but it is not regarded as a serious side effect; (5) a single formulation for all types of acute diarrhoea in all ages facilitates immensely the wide application of this therapy; if required, it would probably be easier to modify the mixing and administration of the fluid than to have separate formulations.

Because infantile diarrhoea, including rotavirus diarrhoea, usually results in stool sodium loss of less than 60 mmol/litre, and because of the concern that a solution containing 90 mmol/litre of sodium might cause hypernatraemia when used to treat infants (particularly those receiving milk formulas), some paediatricians have recommended that the sodium concentration be reduced by administering plain water simultaneously with the 90 mmol/litre solution or by using a solution with a lower sodium concentration. Infants with rotavirus and other non-cholera diarrhoeas have been successfully treated in such a manner.^{6,7}

The necessity for using a less than 90 mmol/litre sodium solution in young infants is not clear. Paediatricians advocating a lower sodium concentration are particularly concerned about the cases of hypernatraemia that have been observed in the past two decades in infants in developed Western countries. However, it is not clear whether these cases related primarily to the sodium concentration of the oral rehydration solutions or to the fact that the infants were receiving a milk formula with excessive carbohydrates which may have caused much intestinal fermentation and osmotic water losses and resulted in voluminous, low sodium stools.⁸ Although immature renal function undoubtedly increases the likelihood of hypernatraemia in young infants, there is some evidence that it is adequate to handle considerable sodium loads by 2 months of age. In any event, infants receiving oral rehydration therapy usually also ingest breast milk (average sodium concentration 7 mmol/litre) or cow's milk (average sodium concentration 22 mmol/litre) and/or some plain water which in themselves dilute the sodium load. One problem with the practice of further diluting the 90 mmol/litre solution with additional water is that this also reduces the concentration of glucose and other electrolytes, such as bicarbonate and potassium, the effect of which is unknown. A potential disadvantage of the use of a lower sodium concentration is that it may in some cases contribute to hyponatraemia, especially in children who have had repeated bouts of diarrhoea, are chronically potassium depleted, and have been given salt-poor fluids or plain water.

Potassium: Potassium absorption is intact during diarrhoea and adequate replacement of potassium loss is particularly important in malnourished children. Potassium concentrations in oral solutions ranging from 0 to 25 mmol/litre have been tested. Marked negative potassium balance with associated hypokalaemia was found in studies employing 0 to 9 mmol/litre. Fluid containing 15 mmol/litre yielded a mean net potassium balance of zero in adults with cholera. Fluid containing 25 mmol/litre

* Patients with severe cholera receiving this solution will generally need to drink about 1.5 times the volume of stool output.

was found to be safe and effective, producing a positive potassium balance in all age groups. No serious problems have been observed with extensive use of a solution containing 20 mmol/litre. In one recent study of infantile diarrhoea, the average faecal potassium concentration loss (29 mmol/litre) was found to exceed that of the oral fluid. One disadvantage of increasing the potassium concentration in the oral fluid is that such solutions may irritate the gastric mucosa and have an unacceptably bitter taste.

Bicarbonate: Bicarbonate is also absorbed during diarrhoea. Clinical studies have established that solutions containing 30 to 48 mmol/litre permit rapid correction of acidosis. Solutions with more bicarbonate may produce mild transient alkalosis but this is of little clinical importance. Bicarbonate also enhances sodium absorption; its omission eliminates the bicarbonate-linked sodium absorption and delays or in severe cases may make impossible the correction of acidosis, thus possibly augmenting the risk of hyperkalaemia associated with acidosis. In one study (unpublished) in which mild to moderately severe adult non-cholera diarrhoea cases were treated with oral rehydration fluid lacking bicarbonate, the serum bicarbonate remained low for a long period in spite of optimal hydration, although no obvious clinical signs of acidosis were observed; the implications of this prolonged acidemia are unknown. Bicarbonate is generally cheap and widely available. A concentration of 30 mmol/litre appears to be effective and safe.

Chloride: The concentration of chloride is determined mainly by the concentrations of salts used. Concentrations of between 80 and 97 mmol/litre have been well tolerated and adequate to replace stool chloride losses.

Glucose (or sucrose): Without glucose (or a suitable alternative substrate) oral salt solutions have been shown to worsen choleraic diarrhoea. Positive gut net balance of water and electrolytes has been achieved with an electrolyte solution containing 1% glucose, but at this concentration the diarrhoea rate increased appreciably. Net absorption was greater with solutions containing 2% glucose, and there was no significant increase in diarrhoea rates. No additional increase in absorption of electrolytes and fluid was observed with solutions containing 3 to 5% glucose and at these concentrations diarrhoea was shown to worsen, presumably due to an increased osmotic load. Since glucose is the most expensive of the chemical ingredients, the lowest concentration that results in maximum absorption (2%) is considered optimum.

Sucrose, which is more readily available but not always cheaper than glucose, has been shown to be an adequate substitute for (i.e., source of) glucose in the treatment of cholera, enterotoxigenic *E. coli* (ETEC) and rotavirus diarrhoeas and diarrhoeas of unknown etiology.^{6,9,10} Balance data showed a tendency towards a slight prolongation of diarrhoea when sucrose was used, especially in severe cases, and particularly in those with cholera. Vomiting also may be more prominent when sucrose is used (10% more episodes), which may be due to increased intake of the sweeter solution. Twice as much sucrose as glucose is needed by weight (4% vs 2%) to yield (if fully hydrolyzed) the optimal glucose concentration; use of 2% sucrose has resulted in an increase in diarrhoea rate, probably due to suboptimal absorption associated with the 1% glucose it can provide.

Fructose is also liberated when sucrose is split, but available evidence suggests that it does not increase fluid and electrolyte absorption during diarrhoea.¹¹

Glucose malabsorption is very uncommon at the 2% concentration (probably less than 1% of cases). Sucrose malabsorption is also uncommon but is more likely to occur. The incidence may vary by country and by season, and is perhaps related to the effects of diarrhoea, dietary sucrose intake (sucrase is an induced enzyme) or changes in nutritional status. When sugar malabsorption is suspected, an analysis should be carried

out to confirm that the composition of the oral fluid is correct and that the excessive stooling rate is not due to osmotic diarrhoea caused by excess sugar concentration. Faulty weighing or mixing of ingredients (either too little or too much) can produce an improper sugar concentration resulting in an increase of diarrhoea and higher failure rates.

In summary, from a physiological standpoint glucose and sucrose are both effective but, where a choice is available, glucose is preferable. The comparative costs of the two ingredients vary greatly from country to country.

Currently recommended composition: It is generally agreed that a single formulation for the fluid to be used for oral rehydration in all acute diarrhoeas, including cholera, in all ages would facilitate the implementation of national rehydration programmes and the widespread application of this simple form of treatment. The evidence accumulated during the last few years continues to support the currently recommended composition as it has been found safe and effective for treatment of acute diarrhoeas.

2.1.2 Evidence of effectiveness of oral rehydration therapy

Oral rehydration therapy in conjunction with sufficient intravenous fluid to correct shock has been clearly shown to reduce mortality to almost zero in cases of severe diarrhoea and to reduce considerably the high cost of treatment associated with hospitalization and use of intravenous therapy alone. This was demonstrated initially in controlled clinical trials in hospitalized adults^{2,3,12} and later in children with cholera and non-cholera diarrhoea.^{4,5} In mild and moderately dehydrated patients oral rehydration therapy without any intravenous fluid has been found highly effective for correcting initial fluid and electrolyte losses as well as for maintaining hydration in the presence of continuing diarrhoea losses. Studies in adults and children with acute diarrhoea caused by cholera and ETEC, and in children with rotavirus diarrhoea, have shown consistent success in achieving and maintaining adequate hydration. Other studies, though limited, have shown that oral rehydration therapy is highly effective also in infants under 3 months of age with diarrhoea. Moreover, there is evidence that oral rehydration therapy can achieve adequate hydration in infants and children with grade II and grade III malnutrition (Gomez classification).⁷⁻¹⁰

Thus it has been shown that, with experience, oral rehydration therapy is usually sufficient for the treatment of all but the most severely dehydrated cases who are in shock or cannot drink and who thus require some intravenous or intragastric administration of fluid and electrolytes. The amount of fluid given initially for rehydration is determined by estimating the degree of dehydration and later, for maintenance, by estimating the volumes of stool, vomitus and insensible water losses.¹³ Failures with oral rehydration therapy are mainly limited to seriously ill cholera patients with an exceptionally high rate of stool output (e.g., more than 12.5 ml/kg/hour) or those few patients with cholera or other diarrhoeas who have persistent intractable vomiting. Mild to moderate degrees of vomiting do not prevent the successful use of oral rehydration therapy.

In addition to its success in hospital-based studies of treatment of cases of the more dehydrating diarrhoeas, oral rehydration therapy has been shown to be efficacious and readily applicable under epidemic situations and in field conditions where resources are limited and medical supervision minimal or absent. Under such conditions oral rehydration fluid can be delivered through the use of patient attendants, who may be instructed by sub-professional health personnel, using thirst as a rough guide. More specific guidelines for administration can also be developed with experience (e.g., administration of about a glassful - approximately 200 ml - of the fluid for each bowel movement or in young children one glass of plain water after two glasses of the oral fluid).

Hospital studies have shown that children who receive early and prompt correction of dehydration, acidosis and potassium depletion with oral rehydration and resume feeding earlier regain the weight loss associated with diarrhoea faster.⁵ A field trial conducted in the Philippines to evaluate the feasibility, acceptability and effectiveness of oral rehydration therapy (here defined as administration of oral rehydration fluid, along with dietary management using available foods) showed that infants and young children treated in this way had a better appetite and gained significantly more weight compared to controls over a seven-month period of observation.¹⁴ Subsequent studies in Turkey, Iran, Egypt and Liberia have shown a similar trend in weight gain in children treated with oral rehydration therapy and dietary management during episodes of acute diarrhoea. Prepackaged ingredients conforming to the WHO-recommended formula were used in all these studies.

One of the greatest advantages of oral rehydration therapy is that it can be brought to the patient's home and administered early in diarrhoea. A number of community-based field studies are now under way to measure the impact of oral rehydration therapy delivered at the village level.

2.1.3 Production and delivery of oral rehydration salts

In recent years many countries have started using oral fluid for the treatment of acute diarrhoeas, particularly in children. The impetus has come from seminars and training courses, national experience with oral rehydration during cholera epidemics, and field studies on the feasibility, acceptability and effectiveness of this form of therapy.

Such attempts at implementation have indicated that there are a number of factors that need to be considered if oral rehydration therapy is to achieve optimal effectiveness. These include: (1) availability of the fluid, (2) acceptability of the fluid, (3) simplicity of use, (4) ability of mothers to make the fluid correctly, (5) affordability for both the individual and the national health service, and (6) chemical and microbiological purity.

In many areas the product is available in the form of packages containing the powdered glucose and salts which are provided by UNICEF directly or through WHO, or produced locally in government laboratories. The production of packages is also being undertaken by the private sector in many countries. In a few areas the supply of prepackaged ingredients has failed to keep up with the demand resulting from promotional and educational activities. Insistence upon the cleanliness and purity of the product and accuracy in measurement is of little value unless the product reaches the people who need and desire it most and they accept and understand how to use it. Because of difficulties in obtaining and maintaining a regular supply of the packages, particularly in remote areas, a few countries have tried to simplify the process by promoting oral rehydration with a solution containing only sugar and salt available in the home. This simplified solution has also been advocated for use in the home in the very early stages of diarrhoea when the complete formula may not be needed and a sodium concentration of less than 90 mmol/litre may be adequate.

The current experiences with production, distribution and preparation are summarized below:

2.1.3.1 Complete formula (sodium chloride, potassium chloride, sodium bicarbonate with glucose/sucrose)

(i) Aluminium foil packs* (UNICEF-type): These packs, which contain dry ingredients of pharmaceutical grade, have a longer shelf-life, permit better quality control and are the most practical technology for widespread distribution if mixing errors can be minimized. They require some sophisticated technology, automation and capital investment for their production and are relatively expensive. Most field studies on the safety and efficacy of oral rehydration have been carried out with this type of product.

(ii) Plastic packs (cottage industry): These packs are usually produced by placing the locally available (generally food, not pharmaceutical, grade) ingredients, weighed in bulk and mixed manually or mechanically, in flame-sealed bags made of polyethylene or other plastic material. They require unskilled labour and unsophisticated machinery for their production and generate local employment. This technology allows for more flexibility in the number and size of the packages and for different volumes of solute. Since the concentration of such ingredients is less accurate than that of pharmaceutical grade ingredients, inaccurate mixing results in a still greater variation of their concentrations; thus great care is needed to reduce mixing errors. Good quality control is not possible. In some packets, the sodium bicarbonate or sugar is packed separately from the other ingredients (split-pack) to prolong the shelf-life. Double packaging, i.e., packing all the ingredients together in two layers of polyethylene has similarly been found useful.

(iii) Locally dispensed ingredients: In some health service facilities the ingredients are weighed and mixed locally and dispensed according to immediate needs in paper, banana leaf or cheap plastic material which may be flame-sealed. Hypodermic syringes or sets of four plastic measuring spoons** have also been used for measuring the different amounts of ingredients in making up such packages. These simple packets have limited durability and are not meant for wide distribution or for storage but they may meet local needs.

2.1.3.2 Incomplete formula (salt and sugar)

This formula generally contains household sugar and salt only and is not packaged. Besides the fact that it generally lacks bicarbonate and potassium, the uncertain amounts and quality of the ingredients are a potential problem, but ready availability of the constituents is an advantage. Domestic teaspoons have been used to prepare the solution in the home, but variations in spoon size have been shown to cause inconsistency in the amounts used. Estimation of the amount of salt with a 2-finger-and-thumb pinch and of sugar by a 4-finger scoop, as is commonly practiced for cooking purposes, has also been advocated; it has similarly been found to give large variations in concentration of the ingredients.¹⁵ The size of the grains, the amount of dampness present, individual dexterity, and different cultural use of the fingers are some of the important factors contributing to the variability. As a possible means of increasing the accuracy of measurements in the home, special plastic two-ended measuring spoons have been devised and are being evaluated.

* At a subsequent WHO Interregional Meeting on the Production of Sachets of Oral Rehydration Salts it was unanimously decided that the ingredients for the fluid must meet the national pharmacopeal standards.

** One such set is available through: Teaching Aid at Low Cost (TALC), c/o Institute of Child Health, 30 Guildford Street, London WC1 1EN, England

2.1.3.3 Reconstitution of oral fluid in the home

Measurement in the home of the volume of water in which the oral rehydration salts (complete formula) are to be dissolved deserves special attention as the size and capacity of the vessels commonly available in rural areas are not uniform. A measure is needed to ensure some degree of accuracy though small variations in concentration can be tolerated, especially when the body's homeostatic mechanism is intact.

Some services supply reconstituted oral rehydration fluid (complete formula) in the correct concentration or in a more concentrated form which requires dilution by the user. An obvious disadvantage of the former is the large weight and volume of the container which makes its transport and distribution difficult. With the concentrated solution there is the risk that it may be given to children in an improperly diluted form. Commercially available, ready-to-drink fluids vary a great deal in composition and are very expensive.

In summary, the cost of providing even the "costliest" package of the ingredients of oral fluid is lower than that of intravenous therapy, hospitalization and treatment with antidiarrhoeal drugs that have no or questionable value (see 2.2). Thus, the cost of packets of the complete formula (4 to 24 US cents per litre packet) cannot reasonably be accepted as the sole justification for adopting as an alternative a less than optimum technology for delivery of oral rehydration salts. In national rehydration programmes countries should attempt to provide pre-packaged ingredients at health centres and at the primary health care level while adopting an education programme on dietetic management, personal and food hygiene, and prompt use of salt and sugar solution in the home in the early stages of diarrhoea employing the simplest and safest method of mixing that is feasible and acceptable.

2.2 Other aspects of clinical management

2.2.1 Intravenous rehydration

When intravenous rehydration is required, the preferred solutions are Ringer's Lactate or a specially prepared Diarrhoea Treatment Solution called DTS (containing per litre: sodium chloride 4g; sodium acetate 6.5g; potassium chloride 1g; glucose 10g).¹³ Intravenous solutions that do not contain bicarbonate and potassium (e.g., normal saline) may be used for initial rehydration of patients in shock, provided diarrhoea rates are not excessive and if oral rehydration with solutions containing bicarbonate and potassium is begun early.

Symptomatic hypoglycaemia is a rare and poorly understood complication of severe childhood diarrhoea and indicates an unfavourable prognosis. It must be recognized and treated adequately; the presence of 1% glucose in intravenous fluid may help to prevent it.

2.2.2 Other pharmaceutical agents

Many of the commonly used antidiarrhoeal medications (e.g., kaolin, paregoric, diphenoxyl hydrochloride with atropine, loperamide) have not been shown to be useful in the management of acute infectious diarrhoea. Antimicrobial agents are beneficial in a few specific circumstances such as severe cholera and Shigella dysentery and their use should be restricted accordingly. They may also be beneficial in severe ETEC diarrhoea in children and in travellers to endemic areas, but this requires further evaluation.

Experiments in animals have indicated that certain licensed drugs may be effective in reducing stool rates in toxin-mediated diarrhoeas such as those due to V. cholerae and ETEC. Such drugs include chlorpromazine, nicotinic acid, salicylates and indo-

methacin. Of these, only chlorpromazine has so far been clinically investigated; the results of preliminary studies on its use in the treatment of cholera in humans are encouraging.¹⁶

2.3 Dietary management

Diarrhoea incidence is higher in bottle-fed infants than in exclusively breast-fed infants living in the same environment. This is primarily due to microbiological contamination of bottle feeds (and other foods consumed by weaning infants) and to the absence of the immunological and other protective factors provided by breast milk.

Diarrhoea is both prolonged and more severe in undernourished children; there is also evidence that undernutrition predisposes to more frequent attacks of diarrhoea. These observations may be related in part to the decrease in gastric acidity and the loss of the normal structure and function of the small intestinal mucosa associated with malnutrition.

Fasting has been shown to reduce intestinal enzyme activity and secretion of gastric acid and to result in flattening of the villous structure; these alterations can be avoided with continued feeding. There is no evidence that "resting the intestine" in acute diarrhoeas is beneficial. Studies show that children with enterotoxin-mediated diarrhoea absorb most nutrients very efficiently. While an excessive amount of fat may be found in the stools, positive net absorption of fat is seen even during acute diarrhoea.

Lactase deficiency - as detected by tolerance tests, enzyme assay or an acid stool (pH below 5) - is generally not of clinical significance and it is not a contra-indication for either continued breast feeding or feeding of milk formulas in the diet. Lactose in the amounts and form usually consumed by young children may be tolerated in spite of lowered enzyme levels. Where clinical symptoms associated with lactose intolerance are suspected, a temporary stoppage for 8 to 10 hours of milk feeds and their resumption in diluted form and in small quantities may be indicated. Breast feeding, however, should always be continued.

Studies have shown that a child with diarrhoea who is properly rehydrated with the complete formula appears to have a better appetite even while fluid is still being lost. Children will continue to take food providing there is a strong desire in mothers to feed them. In all cultures locally available foods appropriate for feeding to infants during diarrhoea can be identified and guidelines for their use made available. Attainment of pre-illness weight following an acute diarrhoeal episode requires several days of extra feeding, but the amount of food and time required are not known.

There are no data to support the value of anabolic steroids, vitamins or appetite stimulants in the dietary management of diarrhoea.

3. RECOMMENDATIONS

After reviewing the currently available knowledge and reports on field experiences, the Group made the following recommendations for research which are described within each category in order of priority. While making these recommendations, the Group did not feel these research activities should in any way preclude the extensive use of oral rehydration therapy and it expressed full agreement with the views of the Advisory Group¹ that there should be immediate implementation of national oral rehydration programmes. Accordingly, the Group also felt it appropriate to make some recommendations regarding the implementation of national programmes including training aspects.

3.1 Research

3.1.1 Composition of oral rehydration fluid

- It is necessary to undertake studies to compare the relative absorbability, efficacy and safety of oral rehydration solutions containing 45 to 60 mmol/litre and 90 mmol/litre of sodium for the treatment of cholera and non-cholera diarrhoea in infants and young children. These studies should include breast-fed and artificially fed children, and groups in which no plain water is given and in which plain water is given ad libitum or in defined proportionate volumes with oral fluid. Since packages containing all the ingredients are used for delivery of fluid to the periphery, and since some persons are advocating additional dilution of the ingredients primarily to lower the sodium concentration, some of these studies should also examine the physiological consequences of diluting the concentration of the other ingredients (potassium, bicarbonate, glucose) besides sodium.

- Since the pathogenesis of rotavirus diarrhoea is different from that of toxin-mediated diarrhoea and is associated with damage to the small intestinal mucosa, there is a need to determine whether glucose is necessary in oral rehydration solution for the treatment of rotavirus diarrhoea.

- Studies are needed to compare the effectiveness of oral fluid containing only sugar and salt (incomplete formula) with that of the complete formula (glucose-sodium-potassium-bicarbonate) in the treatment of diarrhoea cases with different degrees of dehydration.

- As there is a high potassium loss in infantile non-cholera diarrhoea, studies should be carried out to determine if there is any benefit to using solutions with more than 20 mmol/litre of potassium (e.g., increase in appetite, better weight gain, decrease in lethargy, reduction of undesirable side effects of hypokalaemia such as ileus and nephropathy). Such studies should include malnourished children.

- In both cholera and non-cholera patients there appears to be increased absorption of oral fluid and a decrease in the volume and duration of diarrhoea when glycine (110 mmol/litre) is incorporated into glucose-containing oral rehydration solutions. Further observations on the effect of glycine are needed, especially in infantile diarrhoea and particularly at the hospital or treatment centre level, where a reduction in duration could decrease manpower needs and the associated hospitalization costs. There is also a need to determine whether there are other substrates that could enhance sodium absorption by independent mechanisms (e.g., certain amido acids) and that might further reduce diarrhoea rates and oral replacement needs. Those that might be studied include glutamate, proteins such as casein-hydrolysates, and other less costly and readily available dietary foods and carbohydrates such as starches, since it is known that amylase present in the gut during diarrhoea generates glucose readily.

- Since acetate should have a better shelf-life than bicarbonate and is relatively inexpensive, studies should be done to determine whether acetate is absorbed during diarrhoea and can be substituted for bicarbonate in the formulation.

- A comparison of the results obtained with absorbable solutions of different osmolarities would help to clarify the role of osmolarity in replacement solutions.

- Absorption of glucose, sodium, potassium and bicarbonate may follow many pathways which may influence each other. The relative magnitude and effect of these interactions on absorbability are largely unknown and merit further study.

3.1.2 Evidence of effectiveness of oral rehydration therapy

- Studies are needed on the best approaches for the treatment of dehydration in severely malnourished children including the definition of the efficacy of oral rehydration.

- The impact of oral rehydration therapy on the incidence of other non-diarrhoeal illnesses, especially respiratory infections, in infants and children needs definition. Such studies should also compare the impact of both the complete and the incomplete formula.

- The efficacy of oral rehydration solutions in preventing and correcting hypoglycaemia has not been fully documented and needs further evaluation.

- More evidence is needed of the efficacy of oral rehydration therapy in dysentery caused by Shigella dysenteriae type 1.

- The causes and mechanisms of parenteral diarrhoea (i.e., diarrhoea due to or co-existing with non-enteric systemic infection) and the effectiveness of oral rehydration in its treatment need to be investigated.

3.1.3 Production and delivery of oral rehydration fluid

When novel approaches in packaging or delivery are conceived, these should always be carefully evaluated for their feasibility, acceptability and effectiveness. The recommendations for research in this section are felt to be of equally high priority.

3.1.3.1 Production

- Locally applicable technology needs to be developed for mass production of packages at different levels of the health service structure. This includes the exploration of new approaches to packaging using low-cost materials. There is also a need for increased flexibility of packet size provided this would not add unduly to the production costs and that consideration is given to shelf-life and quality control.

- The required quality of the ingredients - e.g., pharmaceutical compared with food-quality grade - needs to be established after testing their chemical quality, including moisture content, and their clinical effectiveness.

- Attention needs to be paid to the development of containers for measuring water (solvent) in the home when preparing oral fluid. Different types of measuring vessels and bags should be tested, including the possibility of packaging the salts in the actual container marked for the volume of water to be added.

3.1.3.2 Delivery

- The comparative acceptability, accuracy and effectiveness of non-packet technologies for use in the home (e.g., special measuring spoons, pinch-and-scoop method, domestic spoons) should be evaluated by field research. It is particularly important to determine the mean and range of sodium concentrations obtained with these various methods of mixing as it may be more suitable for them to have a less than 90 mmol/litre sodium concentration for use in the home early in diarrhoea.

- The effect of use and availability of non-packet technologies (e.g., special measuring spoons) for delivery of oral rehydration in a community on the use of pre-packaged ingredients should be investigated. It is also important to determine whether the introduction and support of these two technologies would create too great a demand on the health care system.

- There is a need for studies of the effectiveness of delivery of packages through the health service infrastructure as compared to availability through non-government sources - e.g., pharmacies, village shops, etc.

- The effectiveness of different methods of health education for the promotion of oral rehydration therapy - e.g., through health services, schools, mass media, etc. - should be compared.

- Operational research should be undertaken to demonstrate the effectiveness of a particular method of delivery as a means of promoting national programmes.

3.1.4 Drug development

- Pilot trials should be carried out of the most promising inhibitors of enterotoxin-induced intestinal secretion (e.g., chlorpromazine, nicotinic acid, salicylates and indomethacin). These trials should study effectiveness, toxicity, dose-route-response relationships, and the feasibility of combining these drugs with oral rehydration treatment. It should also be determined whether the anti-secretory drugs are effective against only one class of enterotoxins (such as enterotoxin of V. cholerae and LT of E. coli) or whether they have a broader spectrum including ST of E. coli, and Shigella and Salmonella enterotoxins, as well as invasive diarrhoea caused by rotavirus or salmonellae.

- Controlled trials of available anti-emetic drugs in diarrhoeal diseases of various etiologies should be performed. These studies should attempt to clarify the basic mechanisms of nausea and vomiting in severe secretory and invasive diarrhoeas, develop anti-emetic drugs and identify microbial products that contribute to these symptoms.

- The search should be continued for drugs that would (a) present, stop and/or reverse the toxin-mediated secretory process in the gut and (b) enhance absorption in either the small intestine or the colon or in both.

- The action of narcotics and their analogues (e.g., diphenoxylate) on intestinal secretion and absorption needs to be determined. Any effect should be evaluated against the consequences of prolonged carriage of pathogens in the gut, as well as toxic side effects.

- The benefit of non-specific absorbents like charcoal, kaolin and pectin, which are commonly used for the treatment of diarrhoea, should be studied in carefully designed clinical trials. Such drugs could have selective abilities to bind certain organisms or their virulence factors, such as enterotoxins.

- GM1 ganglioside specifically binds cholera toxin as well as E. coli LT. GM1 coupled with charcoal (to prevent cell uptake of ganglioside) should be evaluated as a prophylactic and/or therapeutic measure against cholera and ETEC diarrhoea. There should also be a search for other specific receptors for the toxins of other diarrhoeal pathogens.

- Traditional - e.g., herbal - drugs with strong anecdotal evidence of efficacy in the treatment of diarrhoea should be carefully analyzed as to their composition and investigated for actual effectiveness.

3.1.5 Other aspects of clinical management

- An effort should be made to define the optimum concentration of glucose needed in intravenous fluid to prevent hypoglycaemia and its desirable rate of administration, as this remains an unsettled point insofar as the composition of intravenous fluids for use in childhood diarrhoeas is concerned.
- Attention should be given to the development of simplified appropriate laboratory techniques that would enable local treatment centres to detect abnormalities of electrolytes and other solutes in body fluids.
- Better clinical methods for the recognition of electrolyte disorders are needed for a more rational approach to the care of very sick, often comatose, children in remote areas.

3.1.6 Dietary management

- Ways of preventing a deterioration of nutritional status following diarrhoea need to be studied. The most appropriate types of foods and feeding patterns should be determined. Studies defining the utilization and acceptability of common calorie sources during and after diarrhoea would help to improve the calorie density of diets.
- The absorptive capacity of children suffering from diarrhoea with reference to the specific etiology of the illness, and particularly during and after rotavirus and ETEC diarrhoeas, should be investigated by clinical trials, balance studies and assays of digestive enzymes.
- Studies on dietary management of malnourished children with diarrhoea are needed to establish an optimal feeding regime in conjunction with oral rehydration therapy.
- Research on anorexia accompanying diarrhoea is required to document its frequency, elucidate the mechanisms by which it occurs in diarrhoea of specific causes, measure its impact on early feeding and total food intake, and determine whether earlier use of oral rehydration therapy results in improved appetite.
- Studies are needed to determine the cause of increased susceptibility to diarrhoea in malnourished children, with careful documentation of the role of decreased gastric acidity and small intestinal function.
- Socio-anthropological studies are needed to identify useful/positive culture-specific beliefs and traditions about weaning practices and about feeding during diarrhoea, with the objective of finding culturally acceptable messages to encourage feeding; and about intra-family food distribution practices to find ways of encouraging the provision of extra food to the child recovering from diarrhoea.

- Alternative forms of health education should be studied, including training methodology, use of the mass media and action/learning techniques, to determine ways of influencing knowledge, attitudes and practices with regard to continued feeding and the provision of added food in the recovery period, and breast feeding.

3.2 Oral rehydration therapy in country health programmes

3.2.1 Implementation

The pre-eminent role of diarrhoeal disease as a killer and as a perpetuator of malnutrition, and the availability and economic advantages oral rehydration therapy may

offer by reducing mortality and other ill-effects of diarrhoea, are not yet widely appreciated by policy-makers. This lack of appreciation and the failure to accord oral rehydration the priority it deserves are the main factors retarding progress in the development of national diarrhoeal disease control (DDC) programmes in many countries. Although more than 50 countries have already started to use oral rehydration therapy, this has not been done within the framework of well organized national programmes. It is believed that the development of a well coordinated national DDC programme as part of the comprehensive country health programme and as an integral component of primary health care will ensure better utilization of the limited financial and human resources and provide maximum and continued benefit, particularly to the underserved population. The first step, therefore, is to convince policy-makers at the highest level of the need for national commitment and proper planning prior to the implementation of such a programme.

WHO may help in this process by establishing the best possible estimate of the extent of diarrhoea as a health and social problem and by highlighting its contribution to mortality and malnutrition and its costs in terms of human waste and health care expenditure. The contribution a national oral rehydration programme can make towards reducing these costs should be presented in clearly understandable terms to policy-makers, and should include the information that most, if not all, of the expense of implementing the programme can be covered by savings in funds that were previously used for hospitalization and other forms of treatment. Assistance may be provided to countries in obtaining specific data through analyses of existing records and by random surveys.

WHO may also cooperate with Member States in programme formulation, which is a process of analyzing the problem of diarrhoeal diseases, deciding on programme objectives, designing strategies, planning activities, determining logistic and training needs, specifying management responsibilities and suggesting a mechanism for continuous evaluation. UNICEF assistance in meeting the training and logistic needs may also be available (see Annex).

The basic approach for implementation of these programmes at the periphery should be through the existing primary health care infrastructure, especially through the basic health services that provide child care at the community level.

While these programmes must be integrated within the existing national health care structure, the identification of a national worker with authority, competence, motivation and influence to ensure speedy implementation of the DDC programme is extremely important. This person would be responsible for the planning, execution and evaluation of the national programme and for coordination with other national and international agencies such as WHO and UNICEF.

To achieve maximum coverage, it may be desirable to extend beyond the health system and seek cooperation with ministries or departments dealing with education, social affairs, communications, agriculture, family planning, nutrition, community services, etc. The cooperation of school teachers, practitioners of modern and traditional medicine and youth groups may be enlisted to expand the outreach of the formal health system. The services of religious and other volunteer agencies should also be sought.

Extensive training is needed for medical and paramedical personnel and a suitable strategy must be developed for educating mothers and other village-based workers for effective delivery of the treatment at home (see under 2.1.3).

Clinicians in health centres and hospitals should be encouraged to set an example by using oral rehydration and to initiate community studies on implementation of oral rehydration therapy. This would ensure both wide participation of the medical profession in the effort as well as the provision of appropriate training centres for field personnel.

Ideally, a national oral rehydration programme should aim at providing all primary health care (PHC) workers and peripheral health centres with an adequate supply of properly made packages containing the complete formula. In hospitals and health centres the ingredients can be weighed and mixed in bulk for local use, thus reducing the need for packages. Initial packet supplies may be obtained through UNICEF but every attempt should be made to produce packets locally. It should also be possible to obtain the assistance of UNICEF in local production (see Annex). Pharmaceutical firms operating in the public and private sectors should be encouraged to undertake local production of such packages at a low cost and to distribute them extensively - down to the village shop level - at a reasonable price. Cheap and simple polyethylene packets, though having a shorter shelf-life, can also be produced as a cottage industry.

The incomplete formula (household salt and sugar) should be confined to use in the home early in diarrhoeal episodes and should be complemented by education of the mothers to seek medical help, i.e., the packaged complete formula, from a PHC worker or health centre if diarrhoea persists or worsens (see 2.1.3, summary).

There are several parameters that can be used for evaluating oral rehydration therapy programmes; they have been described in the report of the meeting of the Advisory Group on Development of a Programme for Diarrhoeal Diseases Control.¹ Useful parameters for evaluating operational activities include: the proportion of mothers spontaneously making up oral fluid at home or obtaining it from local sources at an early stage of diarrhoea, the amount of oral fluid given as compared with the recommended volume, the quality of the fluid, and the growth in demand for and production of oral rehydration packages over a period of time.

In order to measure the impact of programmes, criteria such as changes in overall mortality rate, diarrhoea-specific mortality rate, number of referrals or hospital admissions and improvement in nutritional parameters may be particularly helpful.

In summary, the Group feels that enough is known about oral rehydration therapy for countries to implement this method now as an appropriate strategy in their country health programmes to reduce mortality due to diarrhoeal diseases and their ill effects especially on nutritional status. The Group also feels that technical cooperation and support from international organizations such as WHO and UNICEF will play a key role in national programme development and implementation. Furthermore, wide implementation of this simple strategy, beginning in 1979, would be a highly appropriate way of commemorating the International Year of the Child (IYC).

3.2.2 Education and training

Since oral rehydration therapy is a somewhat new technology, its integration into national health programmes will require a system of education and training which should reach everyone involved in the delivery of health care.

There is clearly a need to educate the policy-makers and senior administrators not only of health ministries but also of other departments whose services extend to the people in the villages. The education of policy-makers and health planners should take place initially through discussions with technical experts. Once the need for

oral rehydration has been accepted, plans can be made for different levels of training from the national to the peripheral level. At the national level there should initially be seminars and workshops for future trainers (doctors and nurses). WHO may provide a pool of resource persons to assist in this training process.

Appropriate teaching materials, with emphasis on simple field guidelines for paramedical workers, should be developed by WHO. This material may differ in sophistication according to the group being trained and may need to be adapted and translated into national languages.

Training at the provincial and district levels can then be arranged by the national health authorities with the help of these trainers and materials. Those receiving the training should include doctors, nurses, health assistants, village or community health workers, and midwives from hospitals and health centres; other appropriate persons such as agricultural extension workers, home management technicians, teachers, family planning outreach workers, nutrition aides and individuals involved in the delivery of primary health care should also be adequately trained. The training for these different categories of personnel will necessarily differ in content.

There is a special need for re-orientation of members of the medical profession, particularly paediatricians and hospital clinicians, and for education of medical and paramedical students in oral rehydration therapy. Many physicians are not aware and some are not convinced of the benefits of this relatively new development. The subject should be incorporated in the curricula of schools for medical and paramedical students and in their textbooks. Medical, and in particular paediatric associations should be encouraged to disseminate information on this aspect by organizing meetings and seminars. Oral rehydration therapy should also be a part of regular in-service and pre-service training programmes. Pharmaceutical firms manufacturing packages should be encouraged to provide adequate information and promotional messages for doctors. Uninitiated clinicians/paediatricians may be awarded fellowships to work in centres using oral rehydration both in daily practice as well as for research purposes.

Manuals for health and allied community workers should be developed incorporating strong emphasis on oral rehydration as a major life-saving activity of community health workers. Up-to-date information on the techniques of this therapy, clear directives for its practical use in the field and precise means of teaching mothers should be provided. At the municipal and village level, small group sessions and even one-to-one instructions could be arranged with adequate teaching aids.

The mass media should be used to channel information to the public. Simple posters, flip charts, comic books, etc. should be prepared for widespread use. Coverage in magazines and journals and the issue of pamphlets can help in the continuing education programme. Audio-visual materials like slides and short films with messages directed at audiences of different levels - i.e., policy-makers, health workers and particularly mothers - may also be developed.

In establishing and improving training and educational programmes, WHO will be benefitted by an appropriate feedback from ongoing national programmes.

ANNEX

UNICEF ASSISTANCE TO JOINT WHO/UNICEF PROGRAMMES ON ORAL
REHYDRATION THERAPY

UNICEF, recognizing that acute diarrhoea is one of the major causes of morbidity and mortality among infants and young children in developing countries, has given high priority to the implementation of WHO/UNICEF programmes on oral rehydration therapy.

UNICEF assistance to country projects, which are planned in accordance with the recommendations of the WHO Advisory Group on Programme Development, comprises:

- (1) Transfer on as wide a scale as possible of the available information, and education of health personnel, particularly at the village and peri-urban level, on the efficacy and ready availability of this method of treatment.
- (2) A parallel educational effort addressed to mothers.
- (3) Provision, wherever the necessary infrastructure and guarantees of good manufacture and control are available, of equipment and raw materials for local (national or regional) production of packages of ORS (oral rehydration salts) complying with WHO specifications.
- (4) Promotion of and assistance in the widespread distribution of locally produced ORS, not only through organized health channels but also through commercial outlets, with the objective of putting it within the reach of every family.
- (5) Provision of ORS packages from its warehouse in emergency situations, for special operative research projects or in cases when local availability cannot meet established needs for national programmes.
- (6) Advice to governments on worldwide sources and prices of ORS packages. In certain cases, procurement of such packages on behalf of governments on a reimbursable basis.

Requests for assistance should reach UNICEF's Country Representative through normal governmental channels. The full extent and duration of UNICEF assistance should be discussed with the Country Representative in cooperation with the WHO Regional Adviser. Widest assistance would in principle be provided during the first two years, after which period governments should be in a position progressively to ensure themselves the continuation of the operation.

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