TARJA RAUTANEN

Oral Rehydration Therapy of Childhood Diarrhoea in Finland

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ACADEMIC DISSERTATION

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This dissertation is based on the following publications, referred to in the text by Roman numerals.

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I Rautanen T, El-Radhi S, Vesikari T. Clinical experience with a hypotonic oral rehydration solution in acute diarrhoea. Acta Paediatr 1993; 82: 52-4.

II Rautanen T, Kurki S, Vesikari T. Randomised double blind study of hypotonic oral rehydration solution in diarrhoea. Arch Dis Child 1997; 76: 272-4.

III Rautanen T, Salo E, Verkasalo M, Vesikari T. Randomised double blind trial of hypotonic oral rehydration solutions with and without citrate. Arch Dis Child 1994; 70: 44-6.

IV Rautanen T, Isolauri E, Salo E, Vesikari T. Management of acute diarrhoea with low osmolarity oral rehydration solutions and Lactobacillus strain GG. Arch Dis Child 1998; 79: 157-60.

V Rautanen T, Halme S, Vesikari T. Community-based survey of paediatric diarrhoea morbidity and home treatment practices in Finland. Acta Paediatr 1998; 87: 986-90.

VI Vesikari T, Rautanen T, Bonsdorff C-H. Rotavirus gastroenteritis in Finland: burden of disease and epidemiologic features. Acta Paediatr Suppl 1999;426:24-30.

ABBREVIATIONS

AAP	=	American Academy of Pediatrics
CDD	=	Diarrhoeal Diseases Control Programme (WHO)
CDR	=	Division of Diarrhoeal and Acute Respiratory Disease Control (WHO)
CI	=	confidence interval
ESPGAN	=	European Society of Paediatric Gastroenterology and Nutrition
GES	=	glucose electrolyte solution
LGG	=	Lactobacillus casei strain GG
ORS	=	oral rehydration (salts) solution
ORS-WHO	=	ORS with the composition approved by WHO and UNICEF
ORT	=	oral rehydration therapy
SSS	=	sugar-salt solution
UNICEF	=	United Nations Children's Fund
WHO	=	World Health Organization

INTRODUCTION

Diarrhoeal diseases continue to be responsible for one-fourth of all deaths among children under 5 years of age in developing countries (Glass et al. 1996, Gove et al. 1997). In developed countries mortality has dramatically decreased but deaths from diarrhoea, although considered avoidable, are far from unknown (Kilgore et al. 1995, Glass et al. 1996, Ruuska 1991). Morbidity has remained stable, showing no declining trend in developed countries during the last 20 years (Glass et al. 1996). In the absence of effective prevention, the proper treatment of diarrhoea plays a key role in reducing individual suffering and in controlling the costs associated with diarrhoeal diseases in childhood.

The discovery of oral rehydration therapy (ORT) has been considered one of the greatest therapeutic advances in this century (Farthing 1994); its increasing use has already significantly reduced diarrhoeal mortality in developing countries (WHO 1990a, Gove et al. 1997). Although this treatment mode is widely accepted and used in developing countries, there has been more resistance and slower acceptance in the developed world. In the 1990s several investigators have evinced concern over the low use of ORT and the unfavourable practices in the treatment of paediatric diarrhoea still advised by doctors and other health workers (Jenkins et al. 1990, Snyder 1991, Goodburn et al.1991). Some critique and debate on ORT has focused on the composition of oral rehydration solutions (ORS), especially the optimal sodium content. Over the years, studies have been conducted in search of "super-ORS" or improved ORS; more recently their focus has been on the optimal glucose concentration and the osmolarity of these preparations.

The foundation of case management by ORT has always been oral rehydration and the rapid re-introduction of feeding. Drugs have been avoided. The latest development in the treatment of diarrhoea is the use of probiotics, live microbial feed supplements which may promote intestinal health and resistance (Perdigon et al. 1988, Majamaa et al. 1995). Lactic acid bacteria are probiotics which may be beneficial in acute diarrhoea and shorten the duration of episodes (Isolauri et al 1991, Kaila et al. 1992).

The present study aimed to investigate various compositions of ORS for use in Finland, and the combined use of ORT and probiotic therapy in cases of acute paediatric diarrhoea. It has also attempted to form a picture of current home case management practices, particularly ORT, and the significance of acute paediatric diarrhoea in Finland at present.

REVIEW OF THE LITERATURE

HISTORICAL ASPECTS OF THE DEVELOPMENT OF ORAL REHYDRATION SOLUTION

Darrow et al. (1949) and Flett et al. (1949), and, later, Harrison (1954) were the first to suggest that oral solutions containing sodium, chloride, potassium and glucose could be used for the correction of fluid loss in diarrhoea. All these investigators proposed that oral glucose-electrolyte solutions (GES) be given after initial intravenous rehydration to provide maintenance of fluid balance and to compensate for discontinued parenteral infusion. Oral rehydration solutions (ORS) were used for initial rehydration of patients in India during two cholera epidemics in 1952 and 1953 (Chatterjee et al. 1953). Patients with mild cholera were successfully rehydrated by mouth alone with a GES containing sodium (114 mmol/l), potassium (28 mmol/l), and glucose (137 mmol/l), and moderate to severe cases were rehydrated by mouth and per rectum with the same solution.

During the late 1950s and early 1960s the glucose-enhanced uptake of sodium and water was discovered. Fisher and Parsons (1953) reported that in a rat small-intestine preparation a small number of cells were involved in glucose transport from the gut lumen into the submucosal space and that the rest of the cells were impermeable to glucose. This was the first indication of a specific receptor site for glucose uptake. Riklis et al. (1958) showed in perfused guinea pig intestine that active absorption of glucose, galactose and fructose was dependent on the intestinal sodium and potassium concentration. They concluded that this was not due to a change in intestinal permeability but related to linked active transport between cations and sugars in the small intestine. Curran (1960) presented data indicating that water transport across a rat ileum preparation was a passive process dependent on active sodium and chloride transport, and this transport was shown to be significantly affected by the presence of glucose. Curran’s study contributed significantly to defining the physiological mode of action of oral rehydration solutions. Crane (1962 and 1965) reported biophysical evidence of coupled glucose and sodium transport in the mucosal microvillous brush border in the small intestine.

All the above studies were performed in laboratory conditions with animal models. Schedl et al. (1963) showed these hypotheses to apply equally to healthy humans and patients with non-tropical sprue. By a simple perfusion technique they demonstrated that absorption of solutes was markedly enhanced in the human small intestine after the addition of 1 % of glucose in ingested Ringer's solution. Malawer et al. (1965) obtained similar results in healthy men. Taylor et al. (1967) reported an intestinal lavage study in cholera patients showing increased net sodium and water absorption upon inclusion of glucose in the lavage solution. Sladen et al. (1969) carried out detailed studies on glucose, sodium and water absorption in the normal human jejunum. They showed that little or no sodium or water absorption occurred from isotonic saline, but that the addition of glucose to the solution had a significant stimulative effect. Maximum rates of absorption were found from saline solutions with 56-84 mmol/l of glucose. In the same year Sachar et al. (1969) reported that the glucose-enhanced sodium pump in the human small intestine remained intact during a bout of cholera. This was an important finding, giving physiological justification for the use of oral rehydration therapy (ORT).

At the same time a series of clinical studies were under way. Phillips (1964) compared several types of ORS in hospitalised patients with cholera and in healthy volunteers. In careful balance studies he found that the solutions replaced electrolyte losses in cholera and that glucose was essential for sodium and chloride absorption. Hirschorn et al. (1968) perfused glucose-, galactose, and fructose-electrolyte solutions into the intestines of adult cholera patients and observed that the net stool output decreased when glucose was added to the perfusion solution, and increased when glucose was removed. Nalin et al. (1968) showed that patients given GES by intragastric perfusion or oral ingestion after initial intravenous hydration therapy required 80 % less intravenous fluids than controls. The authors suggested that oral rehydration solutions could be used for maintenance therapy in cholera patients and even for initial rehydration in mild cases of cholera (Nalin et al. 1968). Pierce et al. (1968) used intragastric infusion of different glucose-electrolyte solutions to determine whether glucose absorption occurs in cholera patients and whether administration of such solutions would alter stool output in cholera. Positive water balance and reduced net electrolyte loss during ORS infusion was demonstrated. A glucose content of 160 mmol/l performed better than 40 mmol/l while an increase to 220 mmol/l did not improve absorption. The same study group conducted a clinical trial with ORS in adult cholera patients after initial 6-hour intravenous therapy (Pierce et al. 1969). The results were so encouraging that they recommended evaluation of ORT also in children and in non-cholera diarrhoea. Cash et al. (1970a,b) demonstrated that some adult cholera cases could be rehydrated solely with ORT and in all cases the need for intravenous therapy was significantly reduced with this therapy.

In the next several years ORT was more extensively tested and shown to be effective in acute diarrhoea regardless of etiology (Sack et al. 1970, Hirschhorn 1973, Nalin et al. 1979), in hyponatraemic and hypernatraemic diarrhoeal dehydration (Pizarro et al. 1983a), and in paediatric, infantile and even neonatal diarrhoea (Nalin et al. 1971a, Hirschhorn et al. 1972 and 1973, Mahalanabis et al. 1974, De et al. 1975a, Chatterjee et al. 1978, Pizarro et al. 1979 and 1983b). It was also shown that in mild and moderate cases of diarrhoea ORT could replace intravenous fluid therapy (Cash et al. 1970a,b, De et al. 1975a,b). Based on these findings Nalin et al. (1974) recommended that cholera vaccination programmes in developing countries be replaced with ORT treatment programmes. A Lancet editorial in 1975 reviewed experience of ORT so far and recommended its use. The 1975 and 1978 Lancet editorials promoted the use of a single solution with a sodium concentration of 90 mmol/l (the WHO-UNICEF recommended composition). This was a compromise to cover sodium needs in diarrhoeas of different etiology. A higher sodium concentration would possibly be needed in rehydrating cholera patients, and smaller concentrations in treating diarrhoeas of other etiology.

Water absorption tests conducted by Sladen and Dawson (1969) suggested a wide range of optimal glucose concentrations in ORS. Nalin et al. (1971b) recommended a concentration of 110 mmol/l, to meet the needs for optimal absorption and to keep consumption of the most expensive ingredient of ORS to a minimum. The WHO-UNICEF recommended composition contains 111 mmol/l of glucose (WHO 1976). There has been only one change in the composition of the WHO-UNICEF-promoted ORS: replacement of bicarbonate with trisodium citrate. This solution is not in wide use in developed countries, commercial solutions with a lower sodium concentration and high glucose being those mainly used. The high glucose concentration in commercial products is believed to make the taste more appealing to children. The commercially available ORS used in Finland in the 1970s contained 35 mmol/l sodium and 200 mmol/l glucose. Isolauri (1985a) compared this solution with an ORS containing more sodium and less glucose, and showed the latter to be more efficient, a finding which led to an improvement in the composition of commercial ORS used in Finland (Osmosal Novum, Leiras, Finland). The molar compositions of ORS-WHO and those used in Finland up to 1999 are shown in Table 1.

Table 1 The molar compositions (mmol/l) of WHO-recommended oral rehydration solution (ORS) and the commercial ORS used in Finland up to 1999.

	ORS-WHO (Bicarbonate)	ORS-WHO (Citrate)	Osmosal (Old)	Osmosal Novum (Leiras,Finland) In use up to 1999
Sodium	90	90	35	60
Potassium	20	20	13	20
Chloride	80	80	30	50
Bicarbonate	30	-	-	30
Citrate	-	10	-	-
Lactate	-	-	18	-
Glucose	111	111	200	144
Osmolarity (mosmol/l)	331	311	296	304

Recognizing the continuing prominence of the problem of diarrhoeal diseases and the new possibilities for their control, WHO established in 1978 the Diarrhoeal Diseases Control (CDD) Programme. The programme has been fully operational since 1980. At present the division is called Diarrhoeal and Acute Respiratory Disease Control (CDR).

Studies on the effectiveness of ORT have been conducted mainly in developing countries, where it has been used successfully for two decades. Few studies have been conducted in developed countries to show the effectiveness and safety of ORT (Santosham et al. 1982 and 1985a, Tamer et al. 1985, Isolauri 1985a,b, Listernick et al. 1985 and 1986, Vesikari et al. 1987, Leung et al. 1988, Cutting et al. 1989, Elliott et al. 1989a and 1990, Cleghorn et al. 1990, Mackenzie et al. 1991, Issenman et al. 1993). Finland has been active in the field. Isolauri (1985a), as mentioned earlier, compared a low-sodium high-glucose ORS with an

ORS containing more sodium and less glucose. She also compared the improved composition (Osmosal Novum) with ORS-WHO, and found them equally effective. The study also showed that the higher sodium concentration in ORS-WHO resulted in higher sodium excretion in urine and in the stools, indicating that excess sodium given in rehydration with ORS-WHO was removed. Vesikari et al. (1987) showed that ORT was not only as effective a mode of therapy as intravenous rehydration but actually shortened the duration of diarrhoea.

Many factors have emerged to explain resistance to ORT. Paediatric textbooks have until recent years recommended intravenous rehydration, at least if more than mild dehydration or vomiting is present (Nelson Textbook of Paediatrics, 13th edition 1987). In point of fact, dehydration is easily overestimated in developed countries, leading to unnecessary intravenous therapy (Mackenzie et al. 1989). Many health workers, again, believe that oral therapy is more time-consuming than intravenous therapy (Avery et al. 1990). However, hospital admission is more likely and repeated electrolyte and acid-base balance measurements are more often needed if intravenous therapy is started. Intravenous rehydration is believed to be safer, whereas in fact more serious complications and accidents are associated with this approach (Pizarro et al. 1979, 1983ab). A meta-analysis by Gavin et al. (1996) showed that in developed countries the failure rate of ORT is infrequent, less than 4 %. ORT was not associated with iatrogenic electrolyte disturbances and patients rehydrated orally had more favourable outcome on several measures. Weight gain at discharge was either better or the same in five out of six studies in the ORT group as compared to the intravenous therapy group (one study did not report this outcome). In five out of six studies the duration of diarrhoea or length of hospital stay was shorter in the ORT group (one study did not report on these aspects).

Although costs do not necessarily determine the choice of treatment, use of ORT may lead to substantial savings. Listernick et al. (1986) estimated that in the United States the mean cost of an outpatient ORT is 270 US dollars as compared to 2300 US dollars for admitted intravenous therapy.

COMPOSITION OF ORS

Sodium

The earliest GES used to supplement maintenance therapy and caloric intake in the late 1940s and 1950s had a sodium content between 25 and 62 mmol/l (Darrow 1949, Harrison 1954, Finberg 1980). Experimental absorption tests showed that up to a point glucose and sodium absorption increased when the sodium concentration of the intraluminally infused solution was increased (Riklis et al. 1958, Curran et al. 1960, Sladen et al. 1969). Initially the sodium concentrations of the solutions used were between 100 and 140 mmol/l to match the high sodium content of adult cholera stools (Chatterjee 1953, Hirschhorn et al. 1968, Nalin et al. 1968, Pierce et al. 1968 and 1969, Cash et al.1970a,b). Subsequently, sodium content was reduced to 90 mmol/l, to match halfway sodium content of adult and paediatric cholera stools and at the same time to be more appropriate for diarrhoea of other etiology (Sack et al. 1970, Mahalanabis et al. 1970, Hirschorn et al. 1972 and 1973).

WHO has promoted a single solution with this sodium concentration (90 mmol/l) since the mid-1970s, and the single solution concept has been regarded as extremely important for logistic and administrative reasons. Largely for this reason, little research was undertaken in developing countries concerning the optimal sodium content in ORS until the role of osmolarity became an issue. Most clinicians and investigators agreed that a sodium concentration of 90 mmol/l was appropriate (even if not necessarily optimal) for all diarrhoea in developing countries. There was, however, concern that this sodium content was still too high for use in milder cases of diarrhoea in well-nourished children in developed countries or in infants (Aballi 1975, Bart et al. 1976, Finberg et al. 1980 and 1982, Saberi et al. 1983). For use in developed countries ORS with lower sodium concentrations have been evaluated and found effective and safe. Santosham et al. (1982) compared the WHO-recommended ORS with a slightly hypotonic (251 mosmol/l) solution containing 50 mmol/l sodium. Both oral solutions were equally effective in correcting dehydration in well-nourished U.S. children.

Two out of twenty patients receiving ORS-WHO developed periorbital oedema. The sodium excretion in the urine was higher in patients receiving ORS-WHO. Isolauri (1985a) evaluated an isotonic (304 mosmol/l) ORS containing 60 mmol/l sodium against the ORS-WHO. The initial dehydration and metabolic acidosis were corrected equally well in both groups and no cases of hypernatraemia were seen. ORS-WHO resulted in excretion of excess sodium in urine and stools. Excretion in the stools could increase the osmolarity of diarrhoeal stools and increase stool output. The hospital stay was slightly shorter in the ORS-60 than in the ORS-WHO group.

Bhargava et al. (1984) compared the standard WHO-recommended ORS with a slightly hypotonic (270 mosmol/l) solution containing 60 mmol/l sodium given to infants aged 0-3 months in India. The authors found that while both solutions were equally effective in correcting dehydration, the high-sodium solution resulted more often in hypernatraemia, oedema and even convulsions. Eleven out of 22 patients developed hypernatraemia (serum sodium > 150 mmol/l) 8-24 hours after rehydration commenced; nine of these children and another two children with normal serum sodium levels developed periorbital oedema. The majority were excessively irritable. One neonate had generalized convulsions 12 hours after admission (serum sodium level 167 mmol/l).

At present, solutions containing less sodium than recommended in the WHO formula are widely used in developed countries. The American Academy of Pediatrics (AAP) formerly recommended (1985) that solutions with 90 mmol/l of sodium should be used only for rehydration and for maintenance therapy preferably a solution containing 40-60 mmol/l of sodium. In the latest guidelines (1996) the AAP states that ORS with sodium concentrations ranging from 50 to 90 mmol/l have proved the effectiveness of ORT in developed countries in children with non-cholera diarrhoea. Solutions with sodium concentrations ranging from 45 to 50 mmol/l are best suited for maintenance, but can satisfactorily rehydrate otherwise healthy mildly or moderately dehydrated children. In 1992 the European Society for Pediatric

Gastroenterology and Nutrition (ESPGAN) recommended a sodium concentration of 60 mmol/l in ORS for use in infants and children in Europe.

Potassium

Potassium is an essential component of ORS since acute diarrhoea can involve substantial potassium losses (Molla et al. 1981). Studies on ideal potassium concentrations are few. Early studies of GES dealt with a considerable range: Chatterjee (1953) used 28 mmol/l, Phillips (1964) 10 mmol/l, Hirschorn et al. (1968) 6 mmol/l and Pierce et al. 8-9 mmol/l (1968) or 10 mmol/l (1969) of potassium. Nalin et al. (1970) compared different GES with potassium concentrations between 6 and 15 mmol/l, and with different sodium, chloride and carbohydrate contents. The main goal was to determine the impact of glycine on sodium and water absorption. The amount of potassium seemed to play only a minor role in the composition. The authors did however recommend the use of a higher concentration of potassium (15 mmol/l) to avoid hypokalaemia.

In the following years concentrations of 20 mmol/l (Hirschorn et al. 1972, De et al. 1975a), 25 mmol/l (Nalin et al. 1970 and 1971a, De et al. 1975b) and 30 mmol/l (Pizarro 1979) were used. In the final WHO-recommended solution the potassium concentration is 20 mmol/l, which is also that widely used in commercial ORS.

Nalin et al. (1980) compared low and high potassium and sodium concentrations in ORS and concluded that ORS containing a low (20 mmol/l) concentration of potassium may lead to hypokalaemia, at least in malnourished children, and recommended further studies on the efficacy and safety of solutions containing 35 mmol/l of potassium. They showed that the potassium concentration did not affect the rehydrating properties of ORS. Clements et al. (1981) compared a simple sugar-salt solution (SSS) without potassium and base with the standard ORS. All children in the complete formula group and 27 out of 29 in the sugar-salt solution group were successfully rehydrated. Two children receiving the SSS developed hypokalaemia.

Cunha Ferreira (1989) reviewed clinical trials testing different ORS to establish safety margins for the ideal composition in Europe, and concluded that the potassium concentration should be between 20 and 30 mmol/l. The ESPGAN (1992) and AAP (1996) recommendation for potassium is 20 mmol/l.

Chloride

Chloride ions are essential for optimal sodium and glucose co-transport (Fordtran 1975). The total chloride concentration in ORS depends on the total content of sodium and potassium, since these are in the form of chloride salts. If only maximal sodium absorption is sought, chloride should be the only anion used in the ORS (Fordtran 1975). If a base or base precursor is added to the solution to promote correction of acidosis, the chloride concentration will range between 30 and 90 mmol/l, depending on the total content of sodium, potassium and other anions (base precursors) in the solution (Cunha Ferreira 1989). This range is considered adequate (Cunha Ferreira 1989, Farthing 1994). In ORS-WHO the chloride concentration is 80 mmol/l.

Glucose and sucrose

On the basis of detailed absorption studies in the human jejunum by Sladen et al. (1969) and other researches (Malawer et al. 1965, Taylor et al. 1967, Pierce et al. 1968), it was recommended that the glucose concentration in ORS should be between 56 and 160 mmol/l in order to achieve maximum sodium and water absorption. A higher concentration would induce osmotic diarrhoea and a lower concentration could lead to insufficient absorption. Glucose is the most expensive ingredient in ORS and not always readily available in developing countries; as low a concentration as possible was thus desirable. On the other hand the hypothesis was that the higher the glucose concentration, the higher the solute absorption. Higher glucose concentrations were also associated with better taste and nutritional value. WHO and UNICEF agreed to promote a single solution with a glucose concentration of 111 mmol/l (Nalin et al. 1971b).

On the other hand, again, the work of Sladen et al. (1969) and Hirschhorn et al. (1968) had demonstrated that maximum sodium and water absorption was already achieved with a glucose concentration of 56 mmol/l. Torres-Pinedo et al. (1966) showed that during diarrhoea infants may have impaired jejunal absorption of carbohydrates, which may cause osmotic diarrhoea with the risk of hypernatraemia. This was clinically proved in a study aiming to increase the nutritional value of ORS by adding a glucose polymer (Caloreen R) to an ORS with a sodium concentration of 90 mmol/l (Sandhu et al. 1982). The molar concentration of the carbohydrate was 110 mmol/l in vitro, but after hydrolysis in the gut, the glucose concentration rose to 730 mmol/l. One patient developed increased diarrhoea and hypernatraemia with convulsions and the study was discontinued. Verber et al. (1990) and Lindfors et al. (1992) reported cases of hypernatraemia in children given glucose polymers as dietary management during concurrent gastroenteritis and ORS therapy.

A rising incidence of hypernatraemic dehydration in infants in the late 1950s raised concern especially in the US over the high sodium concentration in infant milk formulas. It was subsequently realised that the phenomenon was connected to the high carbohydrate content in milk formulas rather than to their sodium concentration. However, such fears came also to be felt regarding the sodium concentration of oral rehydration solutions, and concentrations in some commercial solutions were reduced to as low as 25 mmol/l, although at the same time the glucose concentration could be as high as 5 % (277 mmol/l) or the glucose polymer content 8 % (Finberg 1980, Meeuwisse 1983). The first Finnish commercial ORS (Osmosal) had a sodium concentration of 35 mmol/l and a glucose concentration of 200 mmol/l. After the study by Isolauri (1985a) the sodium concentration was, as noted, increased to 60 mmol/l and the glucose concentration reduced to 144 mmol/l. The product was renamed Osmosal Novum (Leiras, Finland).

In the late 1980s several experimental studies showed that reduction of glucose concentration increased the efficacy of the ORS (Wapnir et al. 1985, Elliott et al. 1986 and 1989ab, Rolston et al. 1987, Sandhu 1989, Farthing 1989, Hunt et al. 1992). Finberg et al. (1982) and Meeuwisse (1983) expressed concern over high glucose concentrations and related risks as early as 1982 and 1983.

Due to the high cost of glucose, investigators sought alternatives. Sucrose is a carbohydrate which is hydrolysed to glucose and fructose. It is cheaper and readily available in developing countries, and could hence constitute a practical source of glucose in ORS. Moenginah et al. (1975) tested whether sucrose could replace glucose, and their findings suggested that glucose and sucrose were equally effective in rehydrating children with diarrhoea. Nalin (1975) concluded that sucrose is potentially useful but marginally less effective than glucose in treating adult diarrhoea, and should only be used as an alternative in situations where glucose is not available. Nalin et al. (1978) confirmed this in another larger study of oral therapy of infant diarrhoea. Palmer et al. (1977) conducted an extensive comparison of glucose and sucrose in ORT in cholera and other severe diarrhoea patients, and found that the two appeared to be equally effective carbohydrate substrates. Likewise Sack et al. (1978) found sucrose and glucose equally effective in treating infant rotavirus diarrhoea. However, in cholera-like diarrhoea glucose-containing ORS appeared to be relatively, albeit not significantly more successful (Sack et al. 1980). A recent study by Faruque et al. (1996a) showed that a reduced-osmolarity ORS resulted in reduced stool output even though glucose was replaced by sucrose, suggesting that the less costly sucrose might be viable in hypotonic ORS.

Rice ORS and cereal-based ORS

Field (1977) wrote an editorial based on Palmer's study suggesting that starches could equally well be used to promote sodium and water absorption. He also pointed out that other molecules, for example neutral amino acids, sharing the same kind of sodium-coupled absorption mechanism as glucose, could be added in ORS to enhance sodium and water absorption and at the same time increase the nutritional value of the ORS. This was the start in the search for an improved ORS which would not only correct dehydration but could reduce stool volume and shorten the duration of the diarrhoeal episode, goals not achieved with the standard ORS. Many water-soluble organic molecules besides glucose can enhance sodium and water absorption from the small intestine, for example oligosaccharides like maltodextrins, polysaccharides like starch from rice and other cereals, and amino acids like glycine and alanine.

Rice powder is slowly hydrolysed to glucose, amino acids and oligopeptides during digestion. As these components are released into the gut lumen slowly, the osmotic load in the gut remains low at the same time as an optimal amount of glucose is available to enhance sodium and water absorption. Rice powder is cheaper than glucose and readily available in many developing countries. Such considerations gave impulse to a number of attempts to establish whether rice powder could replace glucose in the ORS.

Molla et al. (1982) compared rice powder with sucrose as the carbohydrate constituent in ORS, and concluded that the rice powder electrolyte solution was efficient and safe to use in ORT for acute diarrhoea. Patra et al. (1982a) compared rice ORS to glucose ORS and found that the rice preparation was superior to GES and also had nutritional advantages. El-Mougi et al. (1988) compared rice ORS to ORS-WHO and noted shorter duration of diarrhoea, greater mean weight gain and lower mean amount of ORS intake in the rice ORS as compared with the glucose ORS group.

The patients in these studies were infants, children and adults with cholera and acute non-cholera diarrhoea, but the numbers involved were rather small. To determine the true benefits of rice ORS in relation to ORS-WHO, WHO carried out a meta-analysis using data from all available randomised clinical studies comparing the two solutions (Gore et al. 1992). This overview of 13 clinical trials, involving 1367 children and adults, showed that rice-based ORS reduced stool volume by 32 to 36% in patients with cholera. The duration of diarrhoea was reduced by 12%. However, the feeding schedule in these trials had not been standardised: the type, quantity and timing of food given to the patients differed or were not reported.

Fayad et al. (1993) conducted a randomised controlled trial among 460 children with acute diarrhoea comparing rice ORS and ORS-WHO. The patients were fed an identical diet immediately after correction of dehydration. The group receiving glucose-based ORS had a significantly lower mean stool volume (96 g/kg) than the rice-based ORS group (142 g/kg), and the duration of diarrhoea was shorter. Based on this, WHO continues to recommend glucose-based ORS as the standard, together with early feeding. However, rice ORS can be recommended for cholera patients in any situations where its preparation and use are practical (Bhan et al. 1994).

The ORS packet containing precooked rice is larger than the standard ORS packet and requires more space for storage. The dissolved solution is jellylike, rendering preparation slightly difficult.

A variety of other starches have been tested, including wheat, maize and sorghum (Molla et al. 1989). Their use has been limited by reason of the incompletely developed mechanisms to digest starch in young infants (El-Mougi et al. 1988, Lebenthal et al. 1980, Islam et al. 1994).

Like starches, maltodextrins allow an increase of glucose content in ORS without increasing its osmolarity. In the 1980s WHO-CDD supported several studies on maltodextrin-based ORS in developing countries. It emerged, however, that replacing glucose with maltodextrin offers no advantages in terms of total stool output or duration of diarrhoea (Santos Ocampo et al. 1993, Sack et al. 1994, Bhan et al. 1994, El-Mougi et al. 1996). Maltodextrin seems to be as effective as glucose in older patients, but in infants less than 6 months of age lower levels of pancreatic amylase may cause limited digestion of maltodextrin, leading to the release of fewer glucose molecules than expected.

Other organic carrier molecules

As another approach to improve ORS, the addition to the formulation together with glucose of other organic carriers, especially amino acids and dipeptides, has been investigated in a large number of studies, many supported by WHO. A meta-analysis of seven randomised studies comparing standard ORS and ORS containing glycine in children with acute non-cholera diarrhoea was completed in 1991 (International study group 1991). Adding glycine to the solution brought no advantage over ORS-WHO. Vesikari et al. (1986) and Santosham et al. (1986) had previously shown that the glycine-containing solution was actually poorer, as glycine resulted in osmotic diarrhoea and increased urine excretion. A thorough review by Bhan et al. (1994) yielded the same conclusions. In some studies the addition of L-alanine to ORS improved its rehydrating properties in adult cholera patients (Patra et al. 1989). However, in paediatric diarrhoea this kind of formulation had no beneficial effect on stool output or duration of diarrhoea (Sazawal et al. 1991, Ribeiro et al. 1991, Bhan et al. 1994). Similarly, the addition of L-glutamine to ORS was found to be of no practical value (Ribeiro et al. 1994, Bhan et al. 1994).

Although much effort and time were dedicated to the search of an improved ORS along the lines of the above-mentioned findings, WHO concluded that there was no reason to change from glucose to maltodextrin or amino acids in the ORS formulation (WHO 1994a).

Base or base precursor

Bicarbonate or other base precursors have been important components in early intravenous and oral rehydration solutions, as correction of acidosis related to diarrhoea is one of the major goals of therapy together with correction of dehydration (Powers 1926, Darrow et al. 1949 and 1952, Harrison 1954, Phillips 1964, Hirschhorn et al. 1968). Sladen et al. (1968) and Turnberg et al. (1970) showed that bicarbonate stimulated sodium and water absorption in the healthy human small intestine almost as effectively as glucose. Thus, historically, inclusion of a base or a base precursor in the ORS formula has been regarded as important for both absorption of sodium and water and correction of acidosis.

Originally, bicarbonate was the base used (Phillips 1964, Hirschhorn et al. 1968, Nalin et al. 1968, Pierce et al. 1968). Difficulties with its availability and packaging and its tendency to interact with glucose, especially on exposure to high humidity or heat, led WHO to seek an alternative base (Izgu et al. 1981, Patra et al. 1982b, Rolston et al. 1985). Both acetate and citrate were shown to stimulate water and sodium absorption in the normal human small intestine (Rolston et al. 1986). Both were shown to correct acidosis in acute diarrhoea and to posses better storage properties (Cash 1969, Patra et al. 1982b, Islam et al. 1984a and 1985, Santosham et al. 1985a, Hoffman et al. 1985, Salazar-Lindo et al. 1986). Similarly Leiper et al. (1988) showed that there was no difference between bicarbonate, acetate, lactate and citrate in promoting water absorption. Following these studies WHO has since 1984 recommended the use of citrate as the base precursor in ORS-WHO. Due to this change in the composition, the osmolarity of ORS-WHO was reduced from 331 mosmol/l to 311 mosmol/l.

The development of severe acidosis is likely in cholera due to the high purging rate and substantial bicarbonate losses in the stools. In rotavirus diarrhoea the development of acidosis is also common, whereas in other viral and bacterial diarrhoeas severe acidosis develops infrequently. On the other hand, experimental research has shown that although base or base precursors stimulate absorption in the healthy small intestine, this may not be true in the diseased gut lumen. Rollston et al. (1984) demonstrated that in the rat small intestine, after induction of a secretory state by cholera toxin, acetate and bicarbonate enhanced the secretion of water. Lifshitz et al. (1985) found that in the rat small intestine the addition of bicarbonate in an ORS up to 30 mmol/l did not increase, while 40 mmol/l of bicarbonate actually reduced the net absorption of water. Elliott et al. (1993) obtained similar results in the cholera-toxin-treated rat small intestine: in the secreting intestine inclusion of bicarbonate or citrate in an ORS resulted in greater sodium secretion than did an identical ORS without a base. These findings have raised questions as to whether base or base precursor is at all beneficial in ORS.

Many clinical studies have shown that inclusion of a base or base precursor in an ORS does not improve its rehydrating properties. Recovery from acidosis is hastened, but this may be of little clinical importance. Islam et al. (1984b) compared the ORS-WHO without a base with the traditional bicarbonate-containing ORS-WHO in paediatric diarrhoea. The rehydrating properties of both solutions were similar, but acidosis was more successfully corrected in the group receiving bicarbonate-ORS. Clements et al. (1981) compared a simple sugar-salt solution with the ORS-WHO in infant diarrhoea. All infants were successfully rehydrated but the SSS-group patients had more problems with vomiting, hypokalaemia and hypernatraemia. Elliott et al. (1988) compared a low-sodium high-glucose GES with or without bicarbonate and found similar clinical outcome in both treatment groups. This would suggest that at least in cases of mild and moderate dehydration, proper rehydration, resulting in adequate perfusion and renal compensation, will normalise the acid base balance without an additional base. This is also expected to happen in metabolic acidosis of other etiology, for example moderate diabetic ketoacidosis.

Osmolarity

In ORS sodium chloride and the sugar component are responsible for most of the total osmolar concentration of the solution (Meeuwisse 1983). In the ORS-WHO for example they constitute 70 %. When the ORS-WHO was being advocated main concerns were the right sodium concentration and, to a lesser extent, the glucose concentration. The osmolarity of the solution was more or less a passive outcome of the decisions reached, and became 331 mosmol/l. After replacement of bicarbonate with citrate, the figure was reduced to 311 mosmol/l. The ORS-WHO and the majority of commercially available solutions are hypertonic with respect to human serum, the osmolarity of which ranges between 285 and 300 mosmol/l.

Experimental studies have long demonstrated that hypotonic rather than hypertonic solutions would be optimal for solute and water absorption. Fordtran et al. (1961) noted as far back as 1961 that net water aborption was greater from hypotonic than from isotonic solution in the human jejunum. Leiper et al. (1986) showed that isotonic ORS promoted greater water absorption than hyperosmolar beverages and Hunt et al. (1988) showed that water absorption was highest in the human jejunum from a hypotonic ORS with an osmolarity of 240 mosmol/l and a sodium concentration of 60 mmol/l. Farthing (1989) reviewed disease-related animal models using perfusion of cholera toxin-treated rat small intestine or experimental rotavirus infection of neonatal rats and estimated the optimal osmolarity of ORS to be in the range of 200-250 mmol/l. It can be debated whether addition of a base or base precursor in ORS in the experimental tests of Rollston, Lifshitz and Elliott induced higher secretion due to the increased osmolarity of the solutions. Also the reduced efficacy of ORS with added amino acids may at least partly be related to increased osmolarity of these solutions.

WHO realized the importance of osmolarity in the late 1980s and started to promote research on this area . In Egypt, El-Mougi et al. (1994) in a comparative trial of ORS-WHO with a reduced osmolarity ORS (osmolarity 210 mosmol/l, sodium 60 mmol/l, glucose 75 mmol/l) given to 41 children aged 3 to 24 months with acute gastroenteritis and moderate dehydration, showed a significant (37 %) reduction in stool output in those receiving the hypotonic ORS. Also the consumption of ORS was reduced in the hypotonic ORS group by 16 % and the duration of diarrhoea shortened by 35 %. A multicenter evaluation in Brazil, India, Mexico and Peru of ORS-WHO and a hypotonic ORS (osmolarity 224 mosmol/l, sodium 60 mmol/l, glucose 84 mmol/l) in 447 children aged 1-24 months with acute diarrhoea and signs of dehydration, demonstrated that stool output, total ORS intake and duration of diarrhoea decreased in the hypotonic ORS group (International Study Group 1995). The total stool output was 39 % greater, total ORS intake 18 % greater and duration of diarrhoea 22 % longer in the ORS-WHO group (all differences statistically significant). Faruque et al. (1996a) compared a hypo-osmolar sucrose ORS (osmolality 257 mosmol/kg, sodium 60 mmol/l, sucrose 58 mmol/l) given to 46 children aged 6-30 months with acute diarrhoea and dehydration in Bangladesh with ORS-WHO, and found faecal output to be reduced 30 % in the hypo-osmolar ORS group.

Faruque et al. (1996b) have also tested a hypo-osmolar glucose-ORS (osmolality 249 mosmol/kg, sodium 67 mmol/l, glucose 89 mmol/l) in 63 adult cholera patients and found it to be more efficient than ORS-WHO in preserving net intestinal fluid balance in severe cholera. Stool output was reduced by 29 % within the first 24 hours and 37 % within the first 48 hours in patients receiving the hypo-osmolar ORS. However, some cases of hyponatraemia were associated with the use of this solution. Three of the 34 (8.8 %) patients receiving it had a 24 hour serum sodium concentration less than 125 mmol/l compared to 0/29 in the ORS-WHO group.

Santosham et al. (1996) compared ORS-WHO with a reduced-osmolarity ORS (osmolarity 245 mosmol/l sodium 75 mmol/l, glucose 75 mmol/l) among 190 Egyptian children aged 1 to 24 months with acute diarrhoea and signs of dehydration, and found the reduced-osmolarity ORS to have more beneficial effects compared to ORS-WHO as judged by clinical outcome of diarrhoea. The stool output during rehydration was reduced by 36 % in the reduced-osmolarity ORS group, the risk of vomiting during rehydration was lower and the need for unscheduled administration of intravenous fluids was significantly lower. The investigators supported the use of a reduced-osmolarity ORS in children with acute noncholera diarrhoea. Findings thus suggest that hypotonic ORS is beneficial not only in developed countries but for children with acute non-cholera diarrhoea in developing countries, possibly even in cholera. In point of fact the number of clinical studies conducted in developed countries is small.

Lentidoro et al. (1996) found a reduced-osmolarity ORS (formulated according to ESPGAN criteria) effective in 33 out of 36 children aged 3-24 months in Italy. Shornikova et al. (1997) compared a hypotonic ORS (osmolarity 224 mosmol/l, sodium 60 mmol/l, glucose 84 mmol/l) with ORS-WHO in 123 Karelian children aged 1 to 36 months with a high prevalence of bacterial diarrhoea and mild dehydration, and found them equally efficient. However, after the initial rehydration the patients had been given substantial amounts of other fluids (water and liquids with sugar), and the fact that no differences were seen in the duration of diarrhoea between children receiving ORS-WHO or hypotonic ORS was possibly due to these protocol violations.

EFFECTIVE CASE MANAGEMENT

Oral rehydration therapy

Oral rehydration therapy (ORT), as advocated by WHO, consists in prevention of dehydration through proper treatment of diarrhoea in the home using available home fluids or ORS, and treatment of dehydration due to diarrhoea by means of ORS (WHO 1990a). Use of increased amounts of fluid together with continued feeding and increased breastfeeding effectively prevents dehydration in early diarrhoea. If dehydration develops, it should be properly assessed and corrected. WHO recommends slight overcorrection of dehydration within six hours followed by maintenance according to ongoing losses. The strategy of providing one part of water after every two parts of ORS has been shown to prevent the risk of hypernatraemia in children with non-cholera diarrhoea treated with the WHO-recommended ORS. In fact, this strategy roughly corresponds to full use of a hypotonic ORS containing 60 mmol/l sodium.

Early feeding

Despite of occasional recommendations for rapid reintroduction of feedings in earlier years (Chung et al. 1948, Kunnas et al. 1957), fasting long remained part of the treatment of acute diarrhoea, followed by a gradual reintroduction of feedings (Palmberg 1868, Powers 1926, Darrow 1952, Similä 1975, Hirschhorn 1980). Finally, the fasting approach was found detrimental, leading to prolongation of diarrhoea, poor weight gain and mucosal damage; in contrast, rapid reintroduction of full feedings after proper rehydration and continued breastfeeding even during rehydration were found to lead to fast weight gain and maintenance of weight as well as to shorter duration of diarrhoea (Soeprapto et al. 1979, Rees et al. 1979, Dugdale et al.1982, Brown et al. 1984 and 1988, Isolauri et al. 1985b, 1986 and 1989, Khin-Maung-U et al. 1985, Santosham 1985b).

One reason given for advocating fasting was that milk was presumed to aggravate diarrhoea. However, milk was found to be safe during a diarrhoeal episode, not leading to malabsorption or prolongation (Rees et al. 1979, Dugdale et al. 1982, Isolauri et al. 1986, Chew et al. 1993, Brown et al. 1994). In rare cases patchy lesions in the small-intestinal epithelium during an episode can lead to impaired absorption of lactose, causing osmotic diarrhoea and bacterial colonisation of the small bowel (Torres-Pinedo et al. 1966, Graham et al. 1984, Lembcke et al. 1992).

Fermentation reduces the concentration of lactose in dairy products, thus alleviating lactose malabsorption (Onwulata et al. 1989). Fermentation also increases the amount of easily digested amino acids, making fermented dairy products a good source of nutrients during a diarrhoeal episode (Gurr 1987, Hitchins et al. 1989). These free amino acids may also act as carrier molecules and stimulate sodium-solute transport, promoting rehydration (Desjeux et al. 1977).

At present WHO recommends early reintroduction of full feeding immediately after 6 hours' rehydration in dehydrated patients (WHO 1990a). Breastfeeding should be continued even through the rehydration period. In children who have not yet reached a state of dehydration, feeding should be continued uninterrupted. The milk formula given should be full-strength (WHO 1992a). Children with diarrhoea should even be offered increased amounts of easily digested nutritious food to ensure caloric intake during high purging and reduced absorption. The AAP (1996) recommendations are very similar.

Antimicrobials

According to WHO recommendations, antimicrobials are given only selectively in cases where their use is commonly accepted and beneficial, for example in cholera and shigellosis (WHO 1990a,b). The causative bacterial agent should be known and, if possible, antimicrobial sensitivity determined. In Finland the most common bacterias causing diarrhoea are *Yersinia enterocolitica*, *Campylobacter jejuni* and *Salmonellae*. If antimicrobial therapy is indicated, Yersinia infections are usually treated with co-trimoxazole, Campylobacter infections with erythromycin and Salmonella with fluoroquinolones (Raivio and Siimes 1998).

Symptomatic drugs (antidiarrhoeals)

Voluminous stools and continuous losses during a diarrhoeal episode are common concerns of parents, and an effective antidiarrhoeal drug has been actively sought. So far antidiarrhoeal drugs have evinced no advantages in preventing or correcting dehydration and can in fact cause serious complications and increase the cost of treatment (Bradshaw et al. 1982, Turnberg 1983, Lerman et al. 1988, Saunders 1991, Richards et al. 1993).

Adsorbents like smectite, kaolin and activated charcoal have not been shown to be of value in the routine treament of acute diarrhoea in children; they might be called "stool cosmetics"

(WHO 1990b). Cholestyramine solidifies stools and shortens the duration of diarrhoea without side-effects in developed countries (Isolauri et al. 1985b). In Bangladesh it has been found to reduce stool volumes in paediatric cholera patients by 20 to 34 % and to slightly shorten the duration of diarrhoea. The effect remains, however, marginal in the light of the expenses incurred (Rautanen et al., unpublished data).

Antisecretory drugs like chlorpromazine may cause excessive sedation in children (WHO 1990b). The antimotility drug loperamide reduces stool losses and shortens the duration of diarrhoea when used together with ORT. The effect is not, however, clinically significant (Motala et al. 1990). On the other hand, loperamide may cause drowsiness, paralytic ileus and worsening of dehydration due to pooling of diarrhoeal stools in paralysed intestines in children (Bradshaw et al. 1982, Vesikari et al. 1985a, Motala et al. 1990, Bhutta et al. 1990, WHO 1990b, Schwartz et al. 1991).

Despite such disadvantages, use of unnecessary antimicrobials and antidiarrhoeals is still common and even advised by doctors and pharmacists (Guandalini 1989, Jenkins et al. 1990, Goodburn et al. 1991, Costello et al. 1992, WHO 1993, Haak et al. 1996).

LACTIC ACID BACTERIA IN THE TREATMENT OF DIARRHOEA

As mentioned in the foregoing, fermentation of milk products reduces the risk of lactose malabsorption and increases the amount of easily digested amino acids (Gurr 1987, Onwulata et al. 1989, Hitchins et al. 1989). Fermented milk products also contain lactic acid bacteria which may be beneficial in diarrhoeal diseases. Perdigon et al. (1988) demonstrated that milk fermented with *Lactobacillus casei* or *Lactobacillus acidophilus* improves the immunodefense of the small intestine. Majamaa et al. (1995) also demonstrated that Lactobacilli enhance antibody response to rotavirus and raise the IgA antibody level in the convalescent stage after rotavirus diarrhoea. *Lactobacillus casei* strain GG (LGG) was superior to *Lactobacillus rhamnosus*, *Streptococcus thermophilus* and *Lactobacillus* *bulgaricus* in promoting intestinal immune responses as well as in shortening the duration of diarrhoea (Majamaa et al. 1995). LGG has been found stable to acid and bile and shown to be able to colonise the human intestine (Silva et al. 1987, Goldin et al. 1992). LGG produces an antimicrobial substance which can inhibit the growth of several gram-positive and -negative organisms (Silva et al. 1987). Gorbach et al. (1987) used LGG successfully to control relapsing Clostridium difficile colitis.

Isolauri et al (1991) used LGG in acute paediatric diarrhoea and established that this probiotic therapy reduced the duration of diarrhoea in hospital from 2.4 days to 1.4 days. Rotavirus infection is believed to provoke a biphasic diarrhoea, the first phase being osmotic and the second associated with overgrowth of urease-producing bacteria (Isolauri et al. 1994). It was proposed that LGG therapy counteracts the disturbed microbial balance occurring in rotavirus infection. Shornikova et al. (1997) found that LGG therapy significantly reduced the duration of paediatric rotavirus diarrhoea but not diarrhoea of confirmed bacterial etiology. LGG is also effective in developing countries. Raza et al. (1995) showed that LGG shortened the duration of diarrhoea in Pakistan and Pant et al. (1996) obtained similar results in paediatric diarrhoea in Thailand.

LGG is one of the few lactic acid bacteria species to be studied in placebo-controlled randomised studies. Many other products are being used although they have not been so extensively investigated. A recent review article (Hove et al. 1999) concluded that majority of clinical studies suggest that lactic acid bacteria alleviate acute diarrhoea, especially in infants, while the effect on antibiotic diarrhoea and travellers' diarrhoea is less clear.

HOME TREATMENT OF PAEDIATRIC DIARRHOEA

At the beginning of this century the home treatment of diarrhoea comprised baths, bowel emptying, starvation and special diets (Palmberg 1868, Löfström 1890, Thorpe 1928, Selander 1950, Kramer et al. 1960). In Finland resting of the bowel by starving for one day with subsequent slow reintroduction of feedings and use of low-sodium ORS for rehydration and maintenance were recommended for the home therapy of paediatric gastroenteritis in 1975 (Similä).

The first recommendations in Finland for modern diarrhoea treatment with ORT and continued feeding were given in the early 1980s (Vesikari et al. 1983 and 1985b). Isolauri et al. (1989) evaluated the preadmission management of children with acute gastroenteritis in Tampere University Hospital in 1978-1987. The admission rate among cases referred to the hospital fell from 90 % in 1978 to 57 % in 1987. The mean age of admitted children rose significantly during the study period: the proportion less than 12 months old was reduced from 50 % in 1978 to 26 % in 1987. The ambulatory management of dehydration became well accepted: in 1978 67 % of patients admitted had only mild dehydration; in 1987 35 % of cases had mild, 50 % moderate and 15 % severe dehydration. In 1978 29 % of patients received intravenous fluids as compared to only 7 % in 1987. During the 10-year follow-up preadmission treatment practices improved. Use of oral rehydration solutions before admission rose from 3 % to 29 % and use of antidiarrhoeal drugs declined from 11 % to 3 % . In 1978 67 % of patients were starved as compared to 53 % in 1987.

Since 1987 little information has been gathered in Finland on home case management practices in paediatric diarrhoea. Reports from abroad have prompted concern that home treatment may not be optimal in developed countries. Jenkins et al. (1990) found that in South Wales 36 % of paediatric diarrhoea cases admitted to hospital had received inappropriate treatment before admission, although 95 % of them had been seen by a family doctor. Snyder (1991) found that the practice of the majority of American paediatricians diverged markedly from the recommendations of the American Academy of Pediatrics for oral rehydration therapy and rapid feeding. An interview study by Goodburn et al. (1991) revealed that in Britain one in two pharmacists would recommend inappropriate treatment for paediatric diarrhoea. Instead of recommending ORT alone with continued feeding, they would advise antidiarrhoeal drugs alone or together with ORT and stopping of feeding. Guandalini (1989) estimated that the ratio of ORS needed/sold in 1987 in Italy was only 0.2, this reflecting far from desirable treatment practices.

MAGNITUDE OF THE DIARRHOEAL PROBLEM WORLDWIDE AND IN FINLAND

Diarrhoeal diseases are among the leading causes of death among children in developing countries. Improved case management practices and access to care have made for a reduction in mortality from diarrhoea from 4 million annual deaths in children under five years of age in the 1980s to 2.2 million according to recent estimates (Claeson et al. 1990, Gove et al. 1997). Nevertheless, diarrhoeal diseases are still responsible for one-fourth of all deaths of children less than 5 years in developing countries. Rotavirus infection is estimated to cause 25 % of these deaths, being equivalent to 6 % of all deaths of children under 5 years of age (Cook et al. 1990, Glass et al. 1996).

The reported attack rates of diarrhoea in developing countries range from 2 to 12 episodes per child per year (Guerrant et al. 1990). WHO has estimated that 1300 million diarrhoea episodes took place in children under five in developing countries in 1993. A total of 350 million litres of ORS was produced or imported for the treatment of these episodes (WHO 1994b).

In the United States approximately 300 children die from diarrhoea each year, 20-40 of them from rotavirus diarrhoea (Kilgore et al. 1995, Glass et al. 1996). In Finland, until the 1940s approximately 700 children died annually from acute diarrhoea (Louhivuori et al. 1950); in the 1970s the figure had declined to 53 for the decade (Mäki et al. 1983) and in the period 1981-1985 only 8 children died from acute diarrhoea in Finland (Ruuska 1991).

Although deaths from diarrhoea in developed countries are rare, morbidity remains high (Guerrant et al. 1990). In the United States two prospective studies in the 1950s and in 1976 showed diarrhoeal attack rates in children under five years of age to be 1.9 and 2.0 episodes per child per year, respectively (Dingle et al. 1964, Hughes et al. 1978). A more recent estimate in the United States suggested that children under five years of age experience 1.3-2.3 episodes of diarrhoea each year (Glass et al. 1991), showing that there is no apparent declining trend in the incidence. Glass et al. (1996) estimated that in the United States from 1979 to 1992 hospitalisations due to diarrhoea among children under five averaged 186 000 per year, 55000 of these being due to rotavirus. In Finland during the years 1955-59 there were 1200 to 2200 reported diarrhoeal episodes per month in children less than two years of age. In 1967-71 the number of monthly reported cases had decreased to 800-1500 in the same age group (Mäki et al. 1983). These figures are based on hospital data. Knowledge of community-level morbidity is less. In a prospective vaccination study by Ruuska and Vesikari (1991) the annual diarrhoea incidence rate in children under 3 years of age was 0.35. Joensuu et al. (1997) actively followed a placebo group of 1207 children in another vaccination study and established an annual diarrhoea incidence rate of 0.64 in children under 26 months of age.

In Finland during the 1950s the peak incidence of diarrhoea occurred in late summer, with a smaller peak in the winter and spring (Mäki et al. 1983). In the 1960s the seasonal variation was less but the above-mentioned peaks could be noted (Mäki et al. 1983). Since the 1970s the peak incidence of diarrhoea has been during winter and early spring (Mäki et al. 1983). In 1978 the seasonality of hospital admissions for paediatric diarrhoea followed this pattern: 55 % of diarrhoea cases were admitted between January and May and were related to rotavirus infection (Vesikari et al. 1981). In 1951 a large proportion (43 %) of infant diarrhoea cases were in the age group 0-3 months. In 1978 50 % of hospitalised cases comprised children less than 12 months of age (Isolauri et al. 1989), while in 1987 the proportion of children under 12 months had declined to 26 % (Isolauri et al. 1989). In the 1940s the majority of diarrhoeal deaths were from summer diarrhoea in very young infants, and hypertonic dehydration was common , found in up to 20 % of infants admitted (Louhivuori et al. 1950, Mäki et al. 1983). Nowadays hypertonic dehydration is rare, less than 1 % among cases admitted (Isolauri et al. 1989). These changes in seasonality, age distribution and clinical picture can be explained by changes in diarrhoeal etiology and infant feeding practices (Mäki et al. 1983).

STUDY HYPOTHESIS

The review of literature suggested that the composition of ORS and home therapy of paediatric diarrhoea might not be optimal in Finland. The present study was designed to investigate various compositions of ORS for use in Finland, with special interest in reduced glucose concentration and osmolarity and combined use of ORT and probiotic therapy. It was also sought to form a picture of current home case management practices and the significance of acute paediatric diarrhoea in Finland.

AIMS OF THE STUDY

The purposes of the present study were to search for an improved composition of oral rehydration solutions, to evaluate hypotonic oral rehydration solutions in oral rehydration therapy, to investigate home case management of diarrhoea in children, and to study diarrhoeal morbidity in Finland.

The specific aims were:

1. to establish whether the reduction of total osmolarity and, practically, glucose concentration, in oral rehydration solutions improves rehydrating properties (**I-IV**)

2. to evaluate the importance of a base or base precursor in an oral rehydration solution (**III**)

3. to further investigate the effect of Lactobacillus GG on acute diarrhoea, and to evaluate the optimal timing of its administration in relation to oral rehydration therapy (**IV**)

4. to study the home case management of diarrhoea in children in the Finnish community (**V**)

5. to investigate paediatric morbidity and mortality from acute diarrhoea in Finland (**V-VI**).

MATERIALS AND METHODS

These researches were conducted in five periods between 1991 and 1996. The clinical study population comprised 538 children aged 1 to 36 months hospitalised for acute diarrhoea (duration less than five days in studies **I-III** and less than seven days in study **IV**) at the Departments of Paediatrics, Aurora Hospital, Helsinki or Jorvi Hospital, Espoo. In the study of home case management, 406 healthy children aged 1 to 59 months and their mothers, visiting well-baby or maternity clinics in the City of Espoo were included (**V**).

The retrospective survey of hospitalisations due to diarrhoeal illnesses between 1985 and 1995 in children aged 0-5 years and cases of death from acute diarrhoea in children aged 0-15 years between 1986-1995 was carried out using data obtained from the National Centre of Statistics (**VI**).

STUDY DESIGN

The study design is summarised in Table 2. The first clinical trial was a pilot study to find out if the recommendations of experimental studies suggesting reduction of osmolarity of ORS would prove true in practice (study **I**). The results of this trial were confirmed in another clinical double-blind and randomised study (study **II**). Study **III** was a double-blind randomised clinical study investigating the importance of a base precursor in ORS. Study **IV** further explored the lower limit of the glucose concentration of ORS and combined use of ORT and probiotic therapy. Study **V** was a community-based retrospective questionnaire study of home case management and study **VI** was based on analysis of hospital admission data, data on cases of death from diarrhoea and data on reported cases of rotavirus diarrhoea.

Table 2 Prescription of study design and distribution of patients into different oral rehydration solution (ORS) and Lactobacillus GG (LGG) / placebo treatment groups

	Study Design	Number of patients	Hypotonic ORS	Standard ORS	Hypotonic ORS/no citrate	Ultrahypo-tonic ORS	LGG/ placebo therapy
CLINICAL STUDIES							
Study I	Open	238	103	135	-	-	-
Study II	Double-blind Randomised	70	35	35	-	-	-
Study III	Double-blind Randomised	107	54	-	53	-	-
Study IV	Double-blind Randomised Placebo-controlled	123	59	-	-	64	123
Total		538	251	170	53	64	123
COMMUNITY-BASED STUDY							
Study V	Retrospective questionnaire	406	-	-	-	-	-
STATISTICAL SURVEY							
Study VI	Retrospective survey of statistics	-	-	-	-	-	-

PATIENTS

The selection of patients for hospital treatment was based entirely on clinical criteria, and no child was hospitalised for this study. In 1991, during the study period from January 2 to May 31, 247 children aged 1-35 months were hospitalised for acute diarrhoea at Aurora Hospital, Helsinki, and were recruited for the study (study **I**). Nine patients were excluded from the analysis: one parent refused to give any ORS to her breastfed baby; four patients did not pass any diarrhoeal stools in the hospital; one child had concomitant pyelonephritis; the follow-up data on three chidren were lost. Of the 238 patients who completed the study, 103 were female and 135 male. Between 25 May 1992 and 8 June 1993 at Jorvi Hospital, Espoo, 82 patients meeting the inclusion criteria for the ongoing study needed hospitalisation for acute diarrhoea and were enrolled in the study (study **II**). Twelve patients were excluded because they did not pass any diarrhoeal stools in the hospital. The 70 eligible patients were 5-32 months old; 31 of them were female and 39 male. In 1992, 113 children aged 4 to 35 months were hospitalised for acute diarrhoea between January 23 and July 20 at Aurora Hospital and enrolled in the study (study **III**). Six were subsequently excluded from the analysis: two did not receive the scheduled ORS therapy; one needed intravenous therapy during the initial rehydration period; one had multiple problems (tracheostoma and anal atresy); the follow-up data on two patients were lost. Of the remaining 107 children, 64 were male and 43 female. Between March 14 and July 18, 1993, 133 children aged 2 to 36 months were admitted for acute diarrhoea and enrolled in the study at Aurora Hospital (study **IV**). Ten were excluded from the analysis: one child did not receive the scheduled probiotic therapy; five received intravenous therapy (one of these children had hyponatraemia on admission); three children did not pass any diarrhoeal stools in the hospital; the follow-up data on one child were lost. Of the 123 children who completed the study, sixty-eight were male and fifty-five female. The total number of patients analysed patients was 538 and the male:female ratio was 306:232. The distribution of patients into different studies is summarised in Table 2.

CLINICAL METHODS

All children admitted underwent a standard physical examination, weighing and estimation of the degree of dehydration. Acute weight loss of the child was calculated as the difference between the child's premorbidity weight and the weight observed, whenever a recent premorbidity weight was available. In other cases fluid deficit was estimated according to the clinical signs of dehydration. In study **I** ORS was administered in an amount twice the estimated fluid deficit over the first 6-8 hours of hospital stay. In studies **II-IV** the recommendation was to give one and one third of the estimated fluid deficit during the first 6-8 hours. A nasogastric drip was used where necessary. After the initial rehydration, maintenance hydration was prescribed according to stool output, estimated by the physician on the ward. Normal feeding for age was resumed after the initial 6-8 hours' rehydration period. In study **IV** fermented milk products were excluded from the diet to prevent interference with the bacteriotherapy used in the study. The blood sodium and potassium concentrations and acid-base balance were determined on admission in studies **I-IV**, and daily thereafter during the hospital stay in studies **II-IV**. A stool sample was taken during the hospital stay for the detection of rotavirus. Urine samples were collected from male patients on the morning after initial rehydration to determine the sodium concentration (studies **II-III**) and osmolarity of the urine (study **II**).

Follow-up of patients in the ward included weighing after initial rehydration and daily thereafter during the hospital stay. The exact amount of ORS administered was recorded by the nurses on the ward, who also recorded the timing and characteristics of all stools passed by the children (described as watery, loose or solid), and all vomiting episodes. The last appearance of "watery" stools was taken as the end point for calculation of the duration of the diarrhoea.

The patients were discharged according to the clinical judgement of the attending paediatricians. The length of the hospital stay was not influenced by the study.

ORAL REHYDRATION SOLUTIONS

A total of 538 children completing the study received oral rehydration therapy according to the respective study protocol (Table 2). Thirty-two children (5.9 %) received additional intravenous therapy besides oral therapy during the study. Of those receiving oral fluids 170 were rehydrated with the standard ORS used in Finland (Osmosal Novum RD, Leiras, Finland), with an osmolarity of 304 mosmol/l, sodium concentration of 60 mmol/l and a glucose concentration of 144 mmol/l (studies **I** and **II**). Three hundred and four patients received a hypotonic oral rehydration solution (osmolarity 224 mosmol/l and sodium concentration 60 mmol/l, studies **I-IV**). Of these, 251 received a hypotonic solution with a glucose concentration of 84 mmol/l with base precursor included (studies **I-IV**) and 53 were given a hypotonic solution with a glucose concentration of 64 mmol/l without a base precursor (study **III**). Another 64 children received an ultrahypotonic oral rehydration solution with an osmolarity of 204 mosmol/l, sodium concentration 60 mmol/l and glucose concentration 64 mmol/l, with base included (study **IV**).

The solutions were prepared by the central pharmacy of Helsinki City Hospitals (**I, III-IV**) or Jorvi Hospital pharmacy (**II**), and supplied as dry powders, which were reconstituted in the ward with 500 ml of water. The sachets containing the various solutions were identical in appearance before and after reconstitution, and blindly coded (**II-IV**). The structure of the study **I** was open. The ORS commercially available in Finland (Osmosal Novum RD, Leiras, Finland) was used between January 2 and March 18, 1991. Between March 19 and May 31,1991 the solution was changed to a hypotonic solution prepared by the hospital pharmacy and supplied as a dry powder, to be dissolved in 500 ml of water. The compositions of the solutions are presented in Table 3.

Table 3 Compositions of the oral rehydration solutions (ORS) used in the study

	Standard ORS (Osmosal Novum) Studies I-II	Hypotonic ORS with base Studies I-IV	Hypotonic ORS without base Study III	Ultrahypotonic ORS Study IV
Sodium (mmol/l)	60	60	60	60
Potassium "	20	20	20	20
Chloride "	50	50	80	50
Bicarbonate "	30	-	-	-
Citrate "	-	10	-	10
Glucose "	144	84	64	64
Osmolarity (mosmol/l)	304	224	224	204

PROBIOTIC THERAPY

In study **IV** patients received Lactobacillus strain GG, ATCC 53103 (LGG) probiotic therapy or placebo in addition to the hypotonic ORS (Table 2). The LGG was provided in 1.25 g freeze-dried doses in small plastic bags containing 5 x 10 9 cfu/dose. The placebo preparation contained microcrystalline cellulose powder (Ph. Eur. 2nd ed. II). The powder sachets were packed and supplied by Valio Ltd., Helsinki, Finland. The LGG and placebo bags and powders were identical in appearance. The freeze-dried powders were mixed with 5 ml of water and administered by spoon or via nasogastric tube. Of the 93 patients given LGG, 28 received one single dose at the start of rehydration therapy, and 33 continued to receive LGG twice a day during the whole hospital stay; 32 received an initial dose of placebo and thereafter LGG, and 30 received a placebo preparation throughout the study.

LABORATORY METHODS

Concentrations of serum sodium and potassium, blood acid-base analysis and urine sodium concentration and osmolarity were determined in the hospital laboratories using standard procedures. Rotavirus antigen was demonstrated in stools using a commercial enzyme immunoassay test (Rotazyme R, Abbott Laboratories, in studies **I** and **III,** or Dakopatts, Denmark, in study **IV**), or latex agglutination test (Orion Diagnostica, Espoo, Finland, in study **II**).

COMMUNITY-BASED STUDY (**V**)

In 1996 from 15 to 26 April 1726 mothers with 2230 children under 5 years of age visiting well-baby and maternity clinics in Espoo, Finland, were asked whether any of these children had had diarrhoea during the preceding four months or during the last two weeks. Diarrhoea was defined as at least two watery stools with or without vomiting, fever, abdominal pain, nausea and other symptoms of acute gastroenteritis. All mothers whose children had had diarrhoea during the four first months of the year were given a questionnaire to be voluntarily filled and returned. The questionnaire gathered information on the severity of the diarrhoeal illness, other accompanying diseases, source of information and help if the parent had sought any, use of ORS and other home fluids, feeding practices at home, use of antidiarrhoeal drugs and problems during the episode.

The number of children who had had diarrhoea within the last two weeks was used to calculate two-week diarrhoea prevalence rate. The method of WHO for calculating the two-week diarrhoea incidence rate was adopted: two-week diarrhoea incidence rate = two-week diarrhoea prevalence rate x 14 : (14 + average duration of a diarrhoea episode). Similarly, the seasonally adjusted annual diarrhoea incidence rate per child was calculated according to the WHO methodology, taking into account the proportion of annual diarrhoea episodes expected to occur during the two-week survey period (WHO 1994c).

STUDY ON HOSPITAL ADMISSION AND MORTALITY DATA (**VI**)

Data on hospital admissions for acute gastroenteritis in the age group 0 to 4.99 years of age in the period 1985 to 1995 were obtained from the National Centre of Statistics. The period covered two years (1985-1986) when the ICD-8 diagnostic code was used and 9 years (1987-1995) when the ICD-9 code was used. The search covered diagnosis numbers 000-009 in 1985 and 1986, and numbers 001-009 in the years 1987-1995. Information on each hospitalised case included the age of the child, day of discharge, and the length of hospital stay in days.

Virologically confirmed cases of rotavirus were derived from the records of the Department of Virology, University of Helsinki (since 1976), and from the reported diagnoses throughout Finland since 1985 (courtesy of Dr O. Meurman, University of Turku). Laboratory reports of rotavirus detections were available on a four-weekly basis, corresponding to 13 periods in a year.

Cases of death associated with acute gastroenteritis in 1986-1995 among children under the age of 16 years were also obtained through the National Centre of Statistics. The medical records of such cases were obtained and reviewed, with the permission of the Ministry of Health and the respective hospitals.

STATISTICAL METHODS

Statistical analysis was carried out on an IBM personal computer using the Statistix 3.1 statistical analysis program or with a MacIntosh personal computer using the StatView 4.02 statistical analysis program. The following statistical tests were used when appropriate: chisquare test (**I-III**), two by two tables (**V**), Student's t-test (**I-III**), Mann-Whitney U-test (**I-III**), rank sum two sample test (**III**), analysis of variance (**IV**) and analysis of variance for repeated measures (**IV**). In study **IV** data with skewed distributions were transformed to their natural logarithms to induce normality. The data are presented either as geometric means with 95 % confidence interval or as medians with range. In studies **V** and **VI** observations of frequencies and rates were used.

ETHICS

The respective study protocols were approved by the Ethical Review Committees of the Health Care Centres of Helsinki and Espoo, and Jorvi Hospital (**I-V**). In studies **II-IV** the parents received written and verbal information on the ongoing study before written informed parental consent was obtained. In study **I** standard hospital instructions for diarrhoea treatment and oral therapy were followed. The study design was open and the only intervention was reduction of the glucose content of the oral rehydration solution used in the hospital for 2 1/2 months. Parental consent was thus not deemed necessary. In study **V** parents were informed of the ongoing study and given a questionnaire for later return.

Permission to collect data on admissions due to diarrhoeal illnesses was obtained from the National Centre of Statistics (**VI**). The Ministry of Health and the respective hospitals gave permission to review the patient records of children who had died from acute diarrhoea (**VI**).

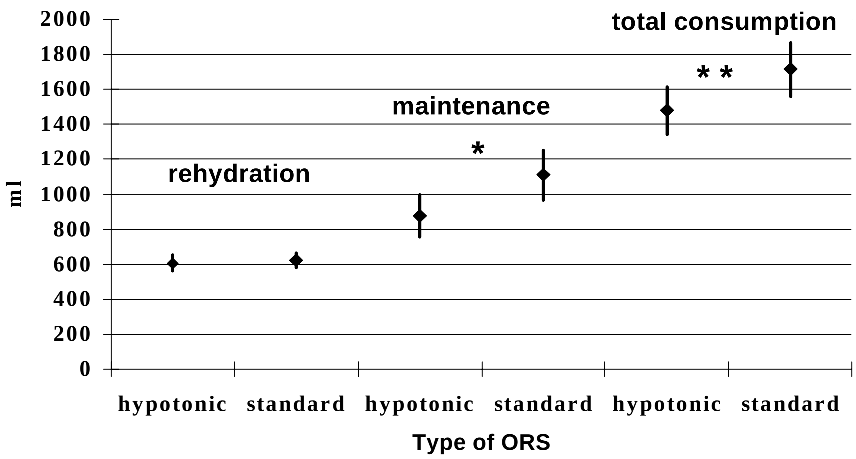
RESULTS

GLUCOSE CONCENTRATION AND OSMOLARITY OF ORS (**I-IV**)

*Hypotonic ORS (**I-III**)*

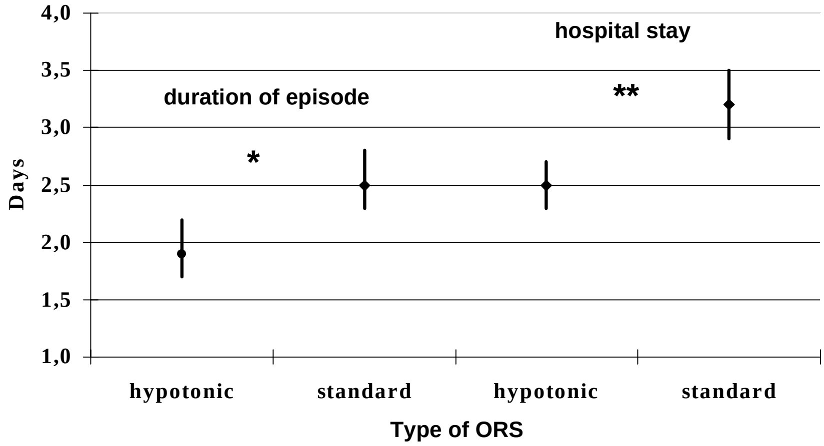
The clinical comparison of the standard (only commercially available) isotonic ORS used in Finland (Osmosal Novum, RD, Leiras, Finland; glucose concentration 144 mmol/l, sodium content 60 mmol/l, osmolarity 304 mosmol/l) and a hypotonic ORS (glucose concentration 84 mmol/l, sodium content 60 mmol/l, osmolarity 224 mosmol/l) was carried out in two trials: in 1991 (**I**) in an open trial in Aurora Hospital, Helsinki, and in 1993 (**II**) in a randomised double blind study in Jorvi Hospital, Espoo. The detailed compositions of the two solutions are shown in Table 3.

In study **I** the groups of patients receiving either of the two rehydration solutions were comparable for age, duration of diarrhoea before admission, degree of dehydration, presence of rotavirus in stools and serum sodium concentration on admission (Table 2/I). The mean (95 % CI) amount of ORS needed for the initial 6-8 hours’ rehydration was similar in the hypotonic and standard ORS groups, 606 (559-652) ml and 621 (580-662) ml, respectively (Figure 1). However, a difference between the groups was observed in favour of those receiving the hypotonic ORS during maintenance therapy. Those given the hypotonic ORS consumed less ORS for maintenance, 874 (755-994) ml versus 1110 (968-1252) ml, p=0.0130, and the mean (95 % CI) total consumption of ORS in the hospital was also less in this group, 1479 (1343-1615) ml versus 1714 (1561-1867) ml, p= 0.0239 (Figure 1). The median number of diarrhoeal stools was 7 in the hypotonic ORS group and 10 in the standard ORS group, p=0.0047, Mann-Whitney U test. Both the duration of diarrhoea in the hospital and the total duration of the hospital stay were shorter in the group receiving hypotonic ORS, 1.9 (1.7-2.2) days versus 2.5 (2.3-2.8) days, p=0.0020 and 2.5 (2.3-2.7) days versus 3.2 (2.9-3.5) days, p=0.0006, respectively (Figure 2). There was no difference in weight gain after rehydration or by discharge in the two groups (Table 3/I). Eight (8 %) infants in the hypotonic ORS group and 16 (12 %) in the standard ORS group were, at some point, given additional intravenous fluids (difference not significant).



***   p=0.0130**
**** p=0.0239**
Two sample t-test

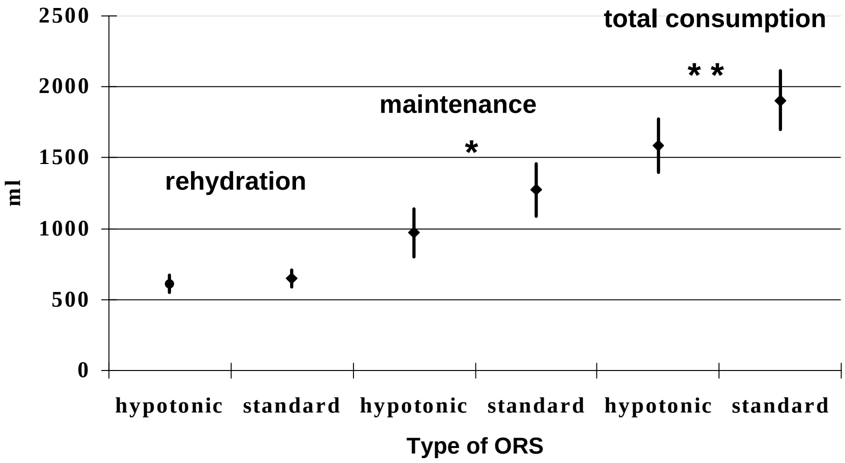
Figure 1 Mean (95 % CI) consumption of oral rehydration solution (ORS, ml) during rehydration, maintenance and total hospital stay among *all* patients (study I)



***   p=0.0020**
**** p=0.0006**
Two sample t-test

Figure 2 Mean (95 % CI) duration of diarrhoea in the hospital (d) and mean (95 % CI) duration of total hospital stay (d) among *all* patients (study I) in hypotonic and standard oral rehydration solution (ORS) groups

The study was undertaken during the peak season for rotavirus diarrhoea, and 79 % of the stool specimens investigated (131 out of 165) were positive for rotavirus. The outcome of these patients was determined separately. The results in the two ORS groups remained very similar in this subgroup. The consumption of ORS for rehydration was equal in the two groups, but during maintenance therapy those receiving the hypotonic solution consumed significantly less ORS solution, 972 (803-1141) ml, than the standard ORS group, 1274 (1089-1459) ml, p=0.0203 (Figure 3). The median number of stools was significantly lower in the same group (9 versus 13 stools, p=0.0099, Mann-Whitney U test). Also the duration of diarrhoea and hospital stay were significantly shortened (Figure 4). There was no difference in weight gain between the groups.



*   p=0.0203
** p=0.0283
Two sample t-test

Figure 3 Mean (95 % CI) consumption of oral rehydration solution (ORS, ml) during rehydration, maintenance and total hospital stay among *rotavirus-positive* (n=131) patients (study I)

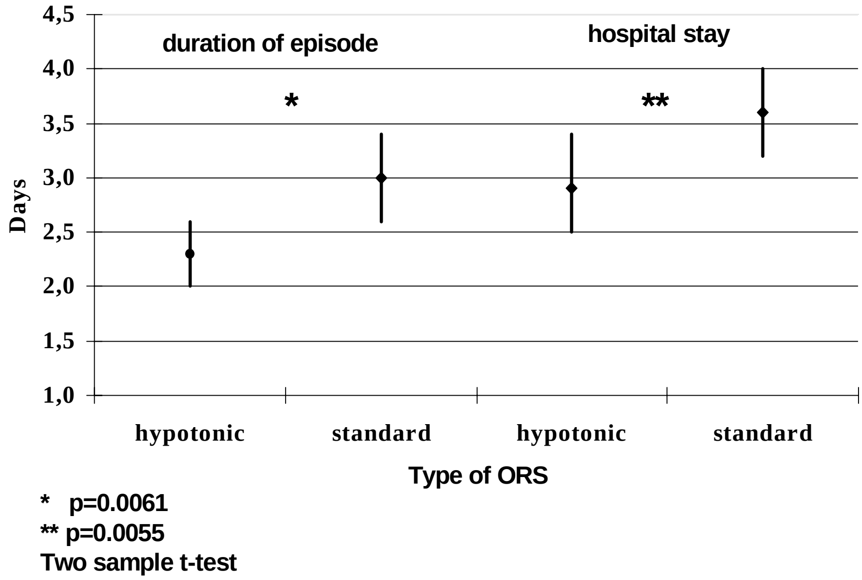
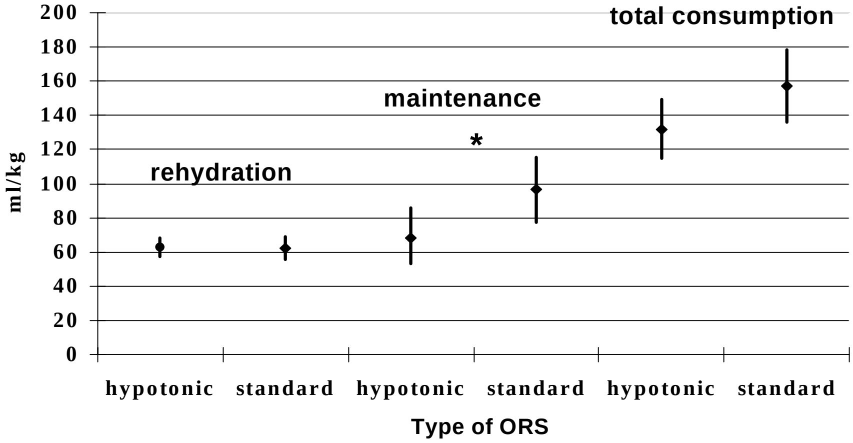


Figure 4 Mean (95 % CI) duration of diarrhoea in the hospital (d) and mean (95 % CI) duration of total hospital stay (d) among *rotavirus-positive* (n=131) patients in hypotonic and standard oral rehydration solution (ORS) groups (study I)

In the double-blind study **II** the two groups receiving the different ORS were comparable for age, duration of diarrhoea before admission, degree of dehydration and serum sodium concentration and acidosis on admission (Table 2/II). The amount of ORS given for initial rehydration did not differ between the groups. The mean (95 % CI) consumption of ORS for rehydration per body weight (admission weight) was 62.7 (57.3-68.1) ml/kg in the hypotonic ORS group and 62.3 (55.6-69.0) ml/kg in the standard ORS group (Figure 5). The amount of ORS given for maintenance therapy, on the other hand, was different in the two groups (Figure 5), the mean (95 % CI) consumption of maintenance fluid being 69.2 (52.4-85.9) ml/kg in the hypotonic ORS group and 96.5 (77.5-115.5) ml/kg in the standard ORS group (p=0.0362). The total ORS consumption in the two groups was 132 (115-149) ml/kg and 157 (136-178) ml/kg, respectively (Figure 5).



* p=0.0362
Two sample t-test

Figure 5 Mean (95 % CI) consumption of oral rehydration solution (ORS, ml/kg) during rehydration, maintenance and total hospital stay among *all* patients (study II)

The median number of diarrhoeal stools passed during hospital stay was smaller in the hypotonic (7 stools) than in the standard ORS group (13 stools) (p=0.0365, Mann-Whitney U test, Table 3/II). The mean duration of diarrhoea in the hospital (44.9 versus 54.4 hours) and total hospital stay (65.6 versus 70.8 hours) were correspondingly shorter in the hypotonic than in the standard ORS group, though the differences did not reach statistical significance (Table 3/II and Figure 6). Weight gain after rehydration and by discharge was similar (Table 2/II).

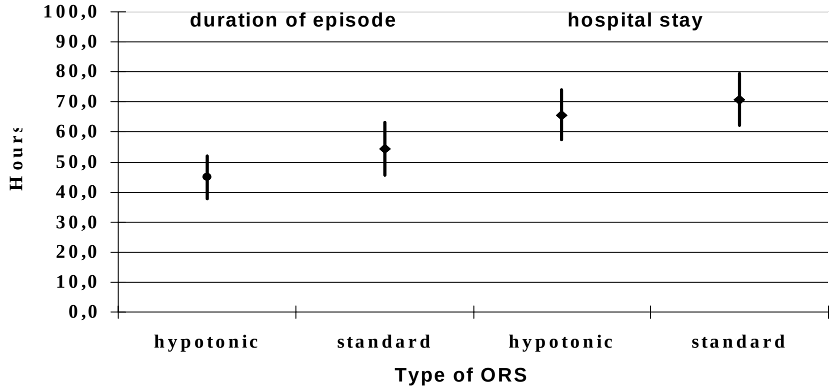
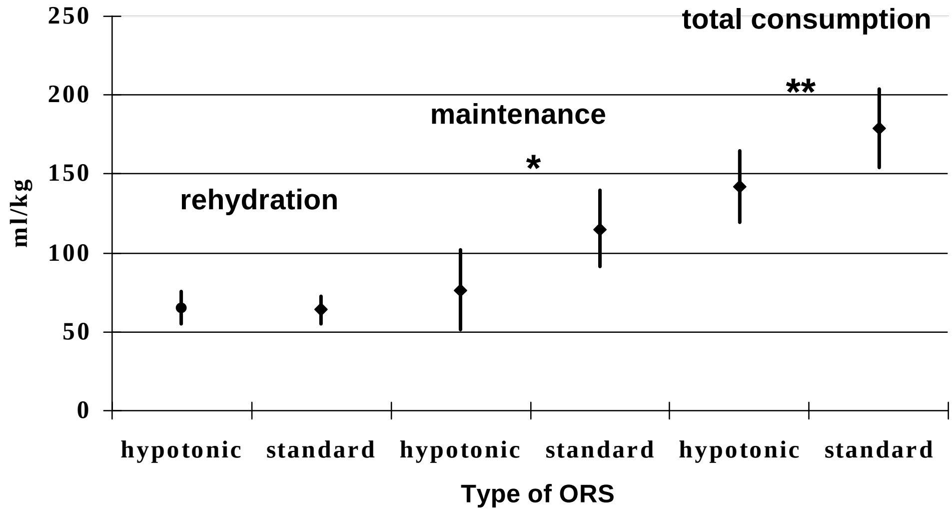


Figure 6 Mean (95% CI) duration of diarrhoea in the hospital (h) and mean (95% CI) duration of total hospital stay (h) among *all* patients in hypotonic and standard oral rehydration solution (ORS) groups (study II)



***   p=0.0384**
**** p=0.0450**
Two sample t-test

Figure 7 Mean (95 % CI) consumption of oral rehydration solution (ORS, ml/kg) during rehydration, maintenance and total hospital stay among *rotavirus-positive* patients (n=40) (study II)

Forty patients (57 %) were positive for rotavirus. The mean number of stools passed, consumption of ORS and duration of diarrhoea show that the disease was more severe in this subgroup. The consumption of ORS during maintenance therapy and throughout the hospital stay was significantly lower in patients receiving the hypotonic ORS than in the standard ORS group (Table 4/II and Figure 7).The median number of stools was 8 in the hypotonic ORS group and 15 in the standard ORS group, however, the difference was not significant (Table 4/II). The duration of diarrhoea and hospital stay were shorter in the hypotonic ORS group, but these differences did not reach statistical significance (Figure 8). Weight gain by discharge was similar.

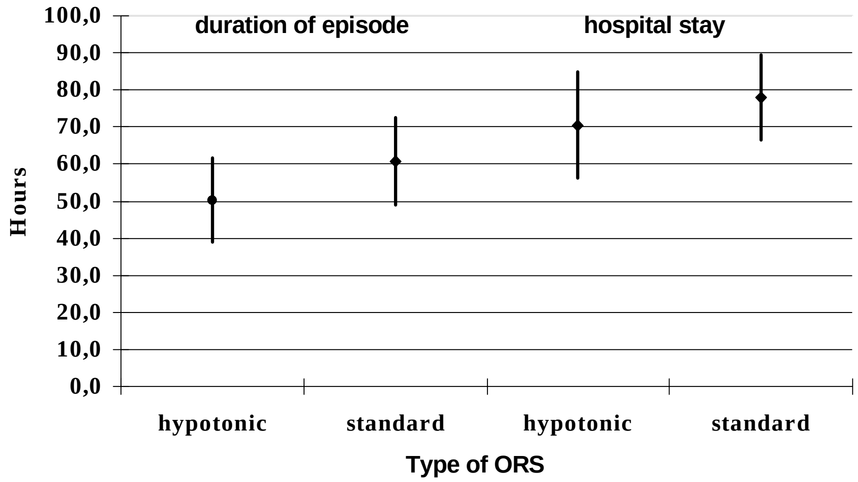


Figure 8 Mean (95% CI) duration of diarrhoea in the hospital (h) and mean (95% CI) duration of total hospital stay (h) among *rotavirus-positive* (n=40) patients in hypotonic and standard oral rehydration solution (ORS) groups (study II)

There were no differences between the groups in electrolyte balance or in recovery from acidosis during the hospital stay (Table 4). Urine sodium excretion and urine osmolarity after rehydration were similar in the two groups (Table 4).

Three patients in the hypotonic ORS group and two in the standard ORS group required intravenous fluids besides the oral therapy (difference not significant).

Table 4 Mean (95 % CI) blood sodium and potassium concentrations (mmol/l), blood base excess (mmol/l), and urine sodium concentration (mmol/l) and osmolarity (mosmol/l) in the two oral rehydration solution (ORS) groups during hospital stay (study **II**)

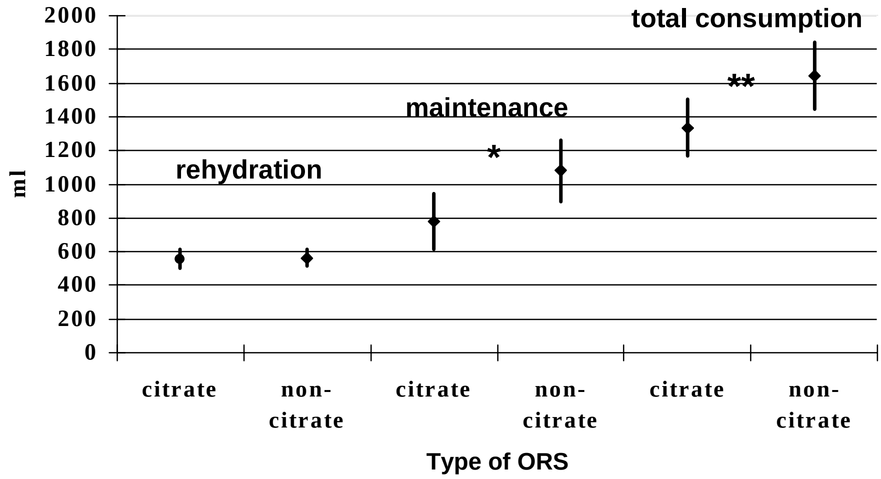
	Hypotonic ORS n=35	Standard ORS n=35
Sodium concentration		
Day 1 (admission)	137 (136-138)	136 (135-137)
Day 2	137 (136-137)	136 (135-137)
Day 3	138 (137-138)	138 (137-139)
Potassium concentration		
Day 1 (admission)	4.1 (3.9-4.2)	4.0 (3.9-4.2)
Day 2	4.4 (4.2-4.5)	4.4 (4.2-4.5)
Day 3	4.4 (4.2-4.6)	4.2 (4.1-4.4)
Base excess		
Day 1 (admission)	-8.5 (-9.8, -7.2)	-9.1 (-10.2, -8.1)
Day 2	-5.3 (-6.6, -4.0)	-4.6 (-5.5, -3.7)
Day 3	-4.1 (-5.4, -2.7)	-4.6 (-5.8, -3.3)
Urine sodium concentration		
Day 2	10.9 (4.4-17.5)	14.7 (8.2-21.1)
Urine osmolarity		
Day 2	289 (189-390)	342 (236-448)

Mean (95 % CI)

Differences between the groups not statistically significant

In study **III** two versions of hypotonic ORS, each with an osmolarity of 224 mosmol/l, with or without citrate, were compared to establish whether a base precursor is essential in the composition of ORS (see also next Chapter "Role of a base precursor in ORS"). One of the formulas contained 60 mmol/l sodium, 84 mmol/l glucose and 10 mmol/l citrate (citrate ORS), the other 60 mmol/l sodium, 64 mmol/l glucose and no citrate (non-citrate ORS). To reach equal osmolarity, the latter formula contained a higher concentration of chloride (the compositions of the two solutions are given in Table 3). The main purpose of this study was to evaluate the role of a base precursor, but it also compared two ORS solutions with different glucose concentrations but the same osmolarity.

The two groups were comparable for duration of diarrhoea before admission to hospital, degree of dehydration, presence of rotavirus in stools, electrolyte balance and degree of acidosis (Table 2/ III). The mean (95 % CI) amounts of ORS given for initial rehydration were almost identical, 557 (502-612) ml and 563 (514-611) ml, respectively (Figure 9). The amounts of ORS needed for maintenance, on the other hand, differed. The mean (95 % CI) consumption of ORS for maintenance was 778 (615-941) ml and 1080 (900-1260) ml in the citrate and non-citrate ORS groups, respectively, p= 0.0130 (Figure 9). The mean (95 % CI) total consumption was 1335 (1166-1504) ml in the citrate ORS group compared with 1643 (1444-1842) ml in the non-citrate ORS group (p=0.0215, Figure 9). Three patients received additional intravenous fluids; two in the citrate and one in the non-citrate ORS group (difference not significant).



***   p=0.0130**
**** p=0.0215**
Rank sum two sample t-test

Figure 9 Mean (95 % CI) consumption of oral rehydration solution (ORS, ml) during rehydration, maintenance and total hospital stay among *all* patients (study III)

The median number of diarrhoeal stools in the hospital was 7.5 in the citrate ORS group and 6 in the non-citrate ORS group (difference not significant). There were no significant differences between the groups in the duration of diarrhoea in the hospital or in the length of hospital stay (Figure 10). There was a small but not significant difference in favour of citrate ORS in the mean (95 % CI) duration of vomiting, 17.1 (11.4-22.8) hours compared to 25.4 (18.2-32.7) hours in the non-citrate ORS group, p=0.0767, Figure 10. The mean (95 % CI) numbers of vomiting episodes were similar, 1.4 (1.0-1.9) and 1.5 (1.1-2.0) episodes in the citrate and non-citrate ORS groups, respectively. Mean (95 % CI) weight gain after initial rehydration was comparable, 197 (136-258) grams and 198 (145-251) grams in the citrate and non-citrate ORS groups, respectively. At the time of discharge the weight gain in the citrate ORS group was slightly but not significantly better, 211 (148-274) grams in the citrate ORS group and 167 (108-226) grams in the non-citrate ORS group, p= 0.3194, two sample t-test.

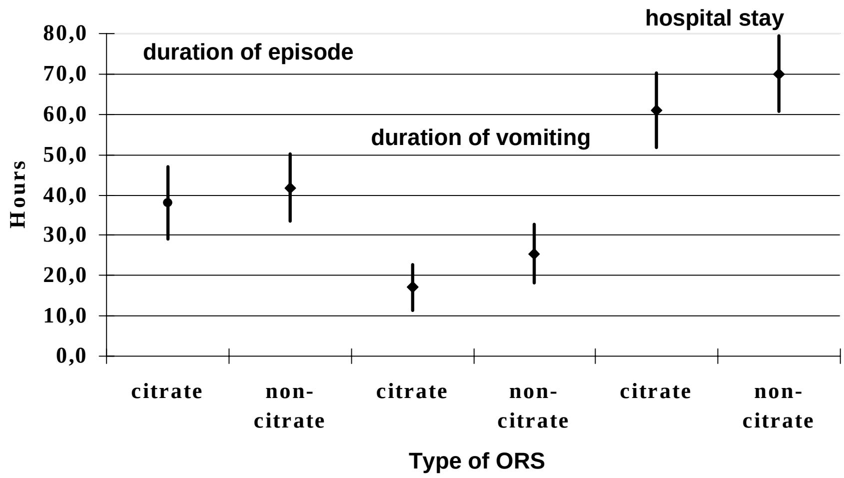
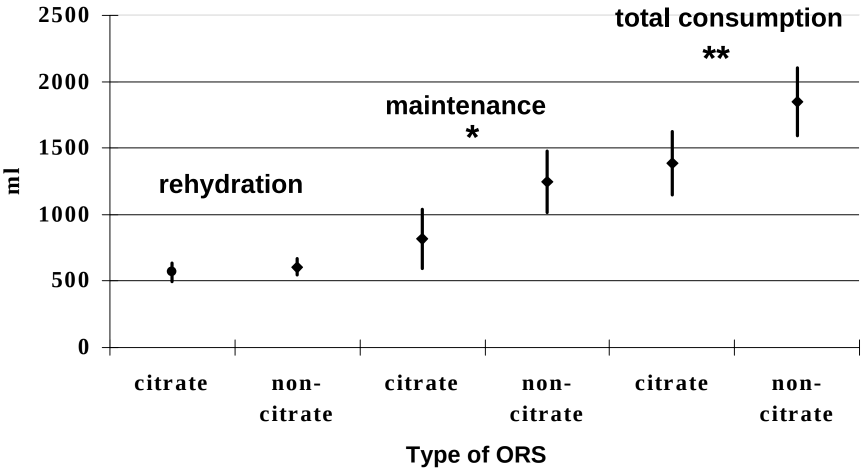


Figure 10 Mean (95% CI) duration of diarrhoea and vomiting in the hospital (h) and mean (95% CI) duration of total hospital stay (h) among *all* patients in citrate and non-citrate oral rehydration solution (ORS) groups (study III)

The rotavirus-positive subgroup (n=66) consumed more ORS. Patients receiving the citrate ORS consumed significantly less ORS for maintenance, 817 (597-1037) ml, and during the whole hospital stay, 1385 (1149-1622) ml, as compared to the non-citrate ORS group, 1244 (1015-1473) ml and 1849 (1594-2104) ml, respectively (Figure 11). The median number of diarrhoeal stools in the hospital was 9 in the citrate ORS group and 7 in the non-citrate ORS group, difference not significant. Duration of vomiting and hospital stay were significantly shorter in the citrate ORS group among rotavirus-positive patients (Figure 12). Weight gain by discharge was 212 (131-293) grams in the citrate ORS group and 119 (52-186) grams in the non-citrate ORS group, p=0.0850, two sample t-test.



*   p=0.0064
** p=0.0079
Rank sum two sample t-test

Figure 11 Mean (95 % CI) consumption of oral rehydration solution (ORS, ml) during rehydration, maintenance and total hospital stay among *rotavirus-positive* (n=66) patients (study III)

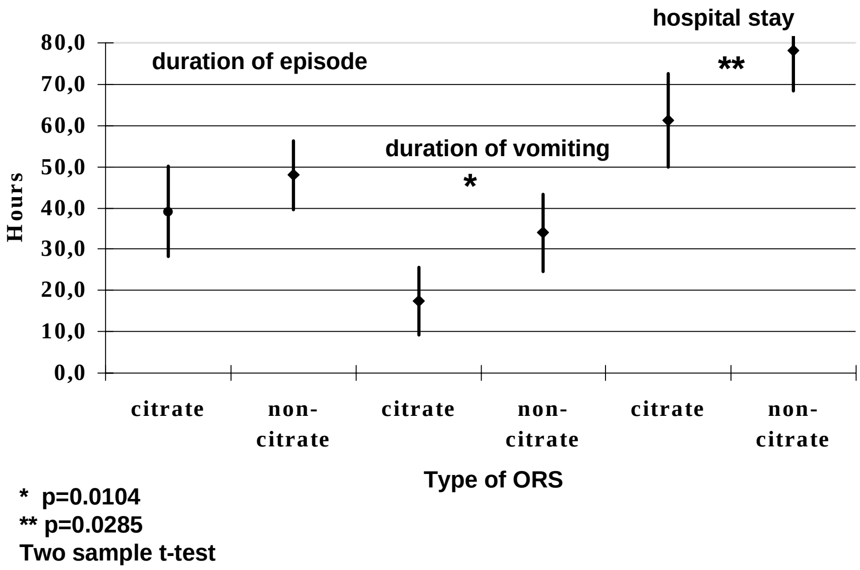
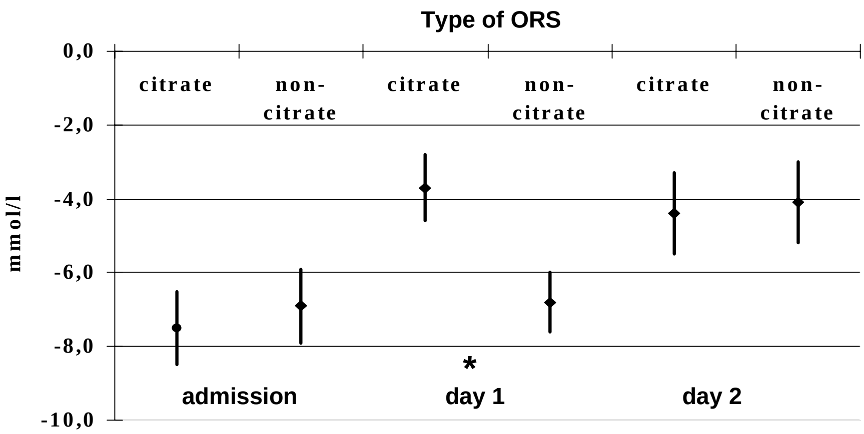


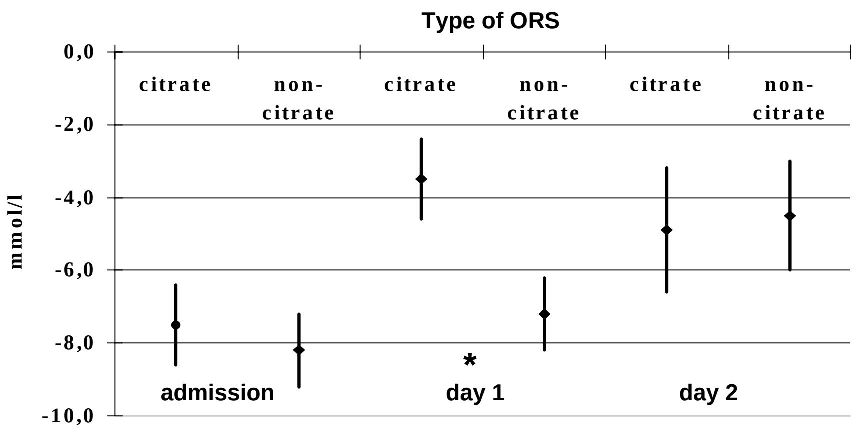
Figure 12 Mean (95 % CI) duration of diarrhoea and vomiting in the hospital (h) and mean (95 % CI) duration of total hospital stay (h) among *rotavirus-positive* (n=66) patients in citrate and non-citrate oral rehydration solution (ORS) groups (study III)

The most significant difference between the groups was in the duration of recovery from acidosis, which was significantly shorter in the citrate ORS group: the mean (95 % CI) base excess on the morning after admission was -3.7 (-4.6, -2.8) mmol /l in those receiving the citrate ORS compared with -6.8 (-7.6, -6.0) mmol/l in those rehydrated with the non-citrate ORS ($p < 0.0001$). On the second morning after admission, however, the degree of acidosis was the same in the two groups: -4.4 (-5.5, -3.3) mmol/l and -4.1 (-5.2, -3.0) mmol/l, Figure 13. The results were similar for rotavirus-positive patients (Figure 14).



*** p<0.0001**
Two sample t-test

Figure 13 Recovery from acidosis among *all* patients in citrate and non-citrate oral rehydration solution (ORS) groups: the mean base excess (mmol/l) on admission, on the morning after admission (day 1) and on the following morning (day 2) (study III)



*** p<0.0001**
Two sample t-test

Figure 14 Recovery from acidosis among *rotavirus-positive* (n=66) patients in citrate and non-citrate oral rehydration solution (ORS) groups: the mean base excess (mmol/l) on admission, on the morning after admission (day 1) and on the following morning (day 2) (study III)

The blood sodium and potassium concentrations did not differ in the two treatment groups during the hospital stay (Table 4/III). The urine sodium concentrations after initial rehydration were similar (38.0 $\pm$ 40.6 mmol/l and 37.2 $\pm$ 33.6 mmol/l in the citrate and non-citrate ORS groups, respectively).

*Ultrahypotonic ORS (**IV**)*

In study **IV** two hypotonic ORS solutions were compared together with oral therapy with Lactobacillus GG (LGG). The two ORS formulas had either a sodium concentration of 60 mmol/l, a glucose concentration of 84 mmol/l and an osmolarity of 224 mosmol/l (hypotonic ORS), or a sodium concentration of 60 mmol/l, glucose 64 mmol/l and osmolarity 204 mosmol/l (ultrahypotonic ORS). The molar compositions of the two solutions are given in Table 3. The age of the patients and the clinical picture on admission were comparable in both ORS groups (Table 3/IV). The two ORS groups did not differ for the presence of rotavirus (95 % and 89 % of patients were positive for rotavirus in the hypotonic and ultrahypotonic ORS groups, respectively), and both groups received as many early LGG therapies (53 % and 47 %, respectively), Table 3/IV.

The consumption of ORS was similar in the two groups during the rehydration and maintenance phases and both ORS corrected dehydration well (Figure 15). Mean (95 % CI) weight gain in hospital was 237 (164-311) grams in the group receiving hypotonic ORS and 186 (112-260) grams in the ultrahypotonic ORS group, but the difference was not significant. There was no difference between the groups in the number of stools passed in the hospital (the mean number of diarrhoeal stools was 8 in both groups). The mean (95 % CI) duration of diarrhoea in the hospital was 23.5 (18.7-29.4) hours in the hypotonic and 30.0 (25.8-34.9) hours in the ultrahypotonic ORS group (p=0.07, Figure 16). The mean duration of hospital stay was the same (47.9 and 49.2 hours, respectively, Figure 16) and blood sodium and potassium concentrations remained similar in the two groups during the hospital stay; recovery from acidosis was equal (Table 5).

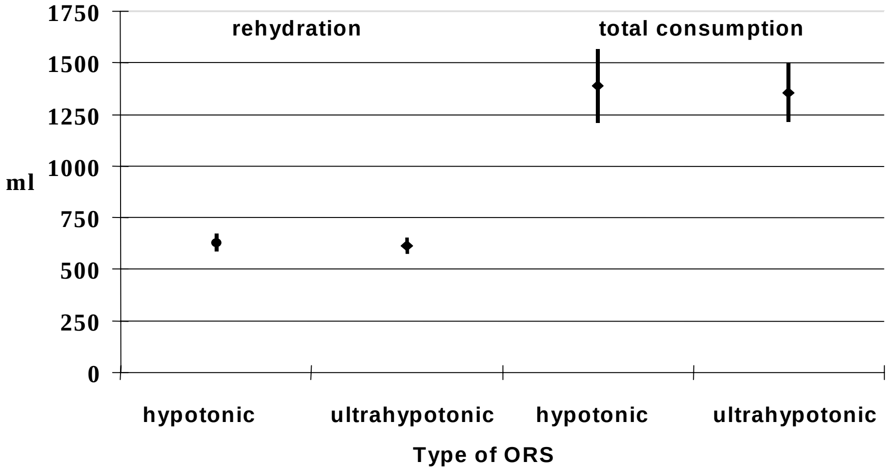


Figure 15 Mean (95% CI) consumption (ml) of oral rehydration solution (ORS, rehydration and total consumption) in hypotonic and ultrahypotonic ORS groups (study IV)

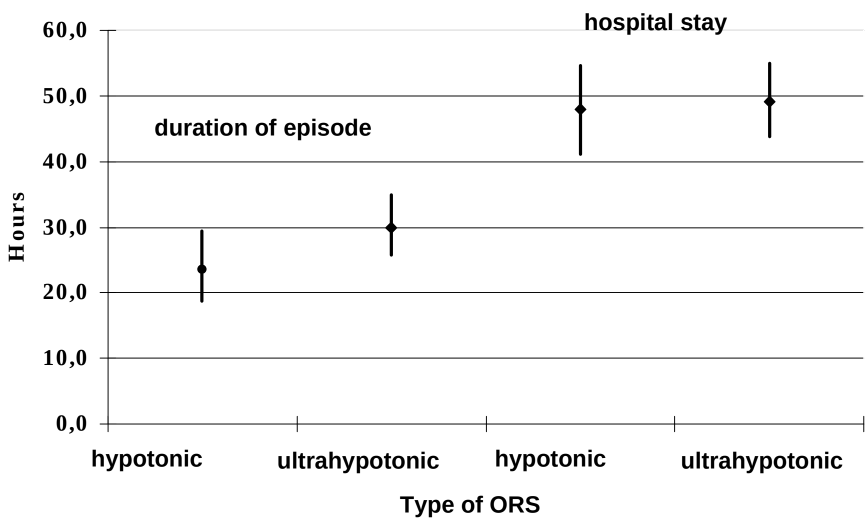


Figure 16 Mean (95% CI) duration of diarrhoea in the hospital (h) and duration of total hospital stay (h) in hypotonic and ultrahypotonic oral rehydration solution (ORS) groups (study IV)

Table 5 Mean (95 % CI) blood sodium and potassium concentrations (mmol/l) and blood base excess (mmol/l) during hospital stay in hypotonic and ultrahypotonic oral rehydration solution (ORS) groups (study **IV**)

	Hypotonic ORS (n=59)	Ultrahypotonic ORS (n=64)
Sodium concentration (mmol/l)		
Day 1 (Admission)	137 (136-138)	137 (136-137)
Day 2	136 (136-137)	136 (136-137)
Day 3	137 (136-139)	137 (136-138)
Potassium concentration (mmol/l)		
Day 1 (Admission)	4.1 (4.0-4.3)	4.2 (4.1-4.3)
Day 2	4.3 (4.2-4.5)	4.5 (4.3-4.6)
Day 3	4.2 (4.0-4.5)	4.2 (4.0-4.4)
Base excess		
Day 1 (Admission)	-7.3 (-8.1, -6.6)	-6.6 (-7.4, -5.8)
Day 2	-3.0 (-3.8,-2.2)	-4.0 (-4.9,-3.1)
Day 3	-2.9 (-4.3,-1.5)	-3.3 (-4.5,-2.1)

Mean (95 % CI)

Differences between the groups not statistically significant

As there were two interventions in the study (ORS therapy and LGG therapy), the outcome of patients was evaluated against both. The mean (95 % CI) duration of diarrhoea was shortest in the subgroup receiving early LGG therapy together with the hypotonic ORS, 17.7 (12.2-25.6) hours, significantly shorter as compared with the other subgroups (Table 4/IV). Both hypotonic ORS and early LGG therapy had an independent effect on the duration of diarrhoea. ANOVA demonstrated that there was also a significant interaction between the two interventions. Best weight gain during rehydration was achieved in the group receiving hypotonic ORS and early LGG therapy, where the mean (95 % CI) weight gain was 262 (170-355) grams; among those receiving ultrahypotonic ORS without LGG, the mean weight gain was 127 (27-227) grams. Hypotonic ORS rather than early LGG therapy was responsible for weight gain during rehydration ($F=3.76$, $p=0.06$ and $F=1.11$, $p=0.29$, respectively); no interaction between the two interventions was observed in this respect.

The best recovery from acidosis was observed in the group receiving hypotonic ORS and early LGG, but the differences did not reach statistical significance (see also the chapter "Probiotic therapy in acute diarrhoea”).

ROLE OF A BASE PRECURSOR IN ORS (**III**)

In study **III** two hypotonic ORS with 224 mmol/l osmolarity, and with or without citrate, were compared in a randomised double blind study (see also previous chapter "Glucose concentration and osmolarity of ORS")). Fifty-four children received the hypotonic citrate ORS and 53 the hypotonic ORS without citrate (the detailed compositions of the two solutions are shown in Table 3). The two groups were comparable for duration of diarrhoea before admission to hospital, degree of dehydration, presence of rotavirus in stools, electrolyte balance and acidosis (Table 2/III).

As noted in the foregoing the mean amounts of ORS given for rehydration were identical in the two ORS groups, but the amounts of ORS needed for maintenance and hence total consumption of ORS were significantly smaller in the citrate ORS group (Figure 9). There was no difference between the groups in weight gain by discharge, in the number of diarrhoeal stools passed in the hospital, in the duration of the diarrhoea in the hospital or in the length of hospital stay (Figure 10). There was a small and not significant difference in favour of citrate ORS in the duration of vomiting (Figure 10).

The most significant difference between the treatments was in the duration of recovery from acidosis, which was significantly shorter in the citrate ORS group; the mean (95 % CI) base excess on the morning after admission was -3.7 (-4.6, -2.8) mmol/l in those receiving the citrate ORS compared with -6.8 (-7.6, -6.0) mmol/l in those rehydrated with the non-citrate ORS ($p<0.0001$, Figure 13). However, by the following morning this difference was no longer significant.

The blood sodium and potassium concentrations and urinary sodium concentrations remained comparable in the two treatment groups during hospital stay (Table 4/III).

PROBIOTIC THERAPY IN ACUTE DIARRHOEA (**IV**)

In study **IV** oral therapy with Lactobacillus GG (LGG) was evaluated together with two hypotonic oral rehydration solutions (see also the foregoing chapter "Glucose concentration and osmolarity of ORS"). Of the 123 patients, 61 received early LGG treatment during rehydration. Of these, 28 received only a single dose and 33 continued to receive LGG twice a day during the whole hospital stay. Of the remaining 62 patients, 32 received an initial dose of placebo, and thereafter LGG, and 30 received only placebo throughout the hospital stay. Both LGG and hypotonic ORS had an independent effect on the duration of diarrhoea (Table 4/ IV). ANOVA demonstrated a significant interaction between the two interventions. The mean (95 % CI) duration of diarrhoea in the subgroup receiving early LGG together with hypotonic ORS was 17.7 (12.2-25.6) hours, significantly shorter as compared with the other subgroups (Table 4/IV). One single early dose of LGG was as effective as LGG therapy continued throughout the hospital stay (Table 6).

Table 6 Duration of diarrhoea (hours) in the hypotonic and ultrahypotonic oral rehydration solution (ORS) and Lactobacillus GG (LGG) groups (study **IV**)

	Hypotonic ORS	Ultrahypotonic ORS
P + P	27.8 (18.9-40.9)	32.9 (23.8-45.6)
P + LGG	32.3 (22.4-46.6.)	27.4 (21.5-35.0)
LGG + P	14.4 (8.0- 26.1)	32.1 (21.3-48.4)
LGG + LGG	21.2 (12.6-35.4)	27.3 (19.7-37.9)

P+P = placebo throughout hospital stay

P+LGG = one early dose of placebo, thereafter LGG

LGG+P = one early dose of LGG, thereafter placebo

LGG+LGG = LGG throughout hospital stay

Mean (95 % CI)

ANOVA:	effect of ORS	F=4.05, p=0.05
	effect of LGG	F=1.55, p=0.21
	interaction	F=2.26, p=0.09

The best weight gain during rehydration was achieved in the same subgroup receiving hypotonic ORS and early LGG therapy, where the mean (95 % CI) gain was 262 (170-355) grams. In the group receiving ultrahypotonic ORS without early LGG, the mean weight gain was 127 (27-227) grams. Hypotonic ORS rather than early LGG therapy was responsible for the gain during rehydration (F=3.76, p=0.06 and F=1.11, p=0.29, respectively); no interaction between the two interventions was observed in this respect.

The best recovery from acidosis was likewise observed in this group, though the differences did not reach statistical significance. The mean base excess after rehydration was -2.8 mmol/l in the said group, higher than in any other treatment groups (Table 7).

Table 7 Effect of type of oral rehydration solution (ORS) and early dose of Lactobacillus GG (LGG) on base excess (mmol/l) after rehydration (study **IV**)

	Hypotonic ORS	Ultrahypotonic ORS
Early dose of LGG received	-2.8 (-3.6, -1.9)	-4.2 (-5.5, -3.0)
No early dose of LGG	-3.3 (-4.6, -2.0)	-3.8 (-5.0, -2.7)

Mean (95 % CI)

ANOVA:	effect of ORS	F=2.76, p=0.10
	effect of LGG	F=0.04, p=0.85
	interaction	F=0.64, p=0.43

There was no difference between the groups receiving early or late LGG with either ORS in the number of diarrhoeal stools passed in hospital (mean number between 7 and 8 in all groups).

HOME CASE MANAGEMENT PRACTICES IN PAEDIATRIC DIARRHOEA (**V**)

Rehydration

At home, as many as 93 % of the 406 children with diarrhoea were offered more fluids than normally. Six per cent were offered as much fluid as normally and only 2 children (1 %) less than normally. ORS was given at home to 150 (37 %) children, including 95 (54 %) of the severe cases. ORS use rates according to age and severity of the diarrhoeal illness are shown in Table 1/V. Younger children below the age of 24 months were significantly more often offered ORS (p=0.001, two by two tables). Of the 20 children eventually admitted to hospital, 14 (70 %) had received ORS before admission. In 107 (26 %) cases ORS was given as a primary fluid (Table 1/V).

Of the 150 children given ORS, 76 (51 %) received it as such and 61 (41 %) received it mixed with other fluids, usually home-made juices. In 57 cases (38 %) dilution probably reduced the efficacy of the fluid (Table 8). The exact amount of ORS given was not known in all cases. However, at least 33 of the 150 ORS recipients received less than 500 ml of ORS, including 24 of the 95 children with severe diarrhoea. Therefore, at most, 29 % of all diarrhoea cases and 40 % of the severe diarrhoea cases were given effective oral rehydration therapy.

Table 8 Mode of oral rehydration solution (ORS) administration to the 150 ORS-recipients (study **V**)

	No. of patients (%)
As such	76 (51%)
Mixed with other fluids	61 (41%)
Dilution acceptable	4 (3 %)
Dilution probably harmful	57 (38%)
Not known	13 (9 %)

Other fluids given during the diarrhoeal episode either as a primary or additional fluid were water, home-made juices, milk, bottled soft drinks and breast milk among others, Table 2/V (ten most frequently given fluids). Many children received more than one type of fluid. Blueberry soup was given to 65 children (16 %), either as a primary or additional fluid. Six children (2 %) were given home-made sugar-salt solutions.

Feeding practices

Of the 406 children 254 (63 %) continued to receive normal food during the diarrhoeal episode, while 138 (34 %) were given a special diet. Of these 138 on changed diet, 62 (15 %) were offered "light" food, 28 (7 %) blueberry-rich diet, 23 (6 %) milk-free diet, 23 (6 %) banana-rich diet, 20 (5 %) increased amounts of sour milk products and 19 (5 %) more liquid diet (Table 3/V). Three per cent of the children were offered more food than normally, 52 % received normal amounts, 43 % were offered less than normally, and 7 % were fasted for at least one day. Thirty-nine (10 %) children were breastfed at the time the diarrhoea started. Of these, 74 % (29 infants) were breastfed more frequently during the episode; the other 10 continued to receive normal amounts of breast milk.

Drug therapy

Associated illnesses were found in 103 children (25 %), mostly respiratory illnesses, including 30 cases of otitis media and three cases of bronchitis. Antibiotics for these other reasons but diarrhoea were given to 36 children (9 %). Other medication was given to 42 children (10 %) during the diarrhoeal episode. Thirty-one children (8 %) received antifebrile medication. Three (0.7 %) were given antidiarrhoeal preparations; two of these preparations originated from abroad. Other medication given included medical carbon (5 cases), dimethicon (1 case) and lactose-reducing drops (1 case).

Products containing lactic acid bacteria were given in 179 cases (44 %). The most common preparation was *Lactobacillus casei* powder (Lactophilus RD, Laboratoires Lyocentre), which was given to 105 children. Dairy products containing *Lactobacillus GG* bacteria (Gefilus RD, Valio Ltd, Helsinki, Finland) were used in 68 cases. Twenty-one children received other lactic acid bacteria preparations, mainly purchased from health food stores (Table 4/V).

Medical consultation

Almost half (48 %) of the children were treated at home without seeking advice. If advice was asked, the main sources of information were relatives and friends (22 %), primary health care physicians (17 %), well-baby clinics (12 %) and private physicians (8 %) (Table 5/V). Altogether 284 (70 %) children were managed at home. Sixty-seven (17 %) visited a primary health care center doctor, 29 (7 %) a private doctor, 45 (11 %) hospital emergency clinic and 20 (5 %) were hospitalised. Children under two years of age were significantly more often taken to the hospital emergency clinic and admitted to hospital (p=0.003 and 0.01, respectively, two by two tables), as compared to older children.

Other problems

Common problems perceived by the mothers during the diarrhoea episodes are shown in Table 6/V. One in three mothers (34 %) felt the greatest problem during diarrhoea to be to make the child drink. Sixteen per cent of the mothers had difficulties in getting the child to eat. Twelve per cent of the mothers were afraid they might not detect signs of dehydration.

MORBIDITY DUE TO DIARRHOEA (**V-VI**)

*Community-based data (**V**)*

The 1726 parents who attended the well-baby and maternity clinics during the study period had altogether 2230 children under 5 years of age. Of these, 473 had suffered at least one episode of diarrhoea within the first 4 months of the year 1996 (13 children had had two and 2 children three episodes during this period), and 111 had had diarrhoea within the last two weeks. The two-week diarrhoea prevalence was calculated from the 111 diarrhoea episodes occurring during the preceding two weeks, and was 5.0 %. This was converted to two-week diarrhoea incidence following the WHO methodology. As the mean duration of a diarrhoea episode was 4.8 days, the two-week diarrhoea incidence was 3.7 %. The seasonally adjusted annual diarrhoea incidence rate was 0.48 episodes per child per year.

The 473 children with diarrhoea belonged to 383 mothers. Of these mothers, 345 returned the questionnaire on home case management practices, this corresponding to 406 children. The six-monthly age distribution of these cases is shown in Figure 2/V. The diarrhoea prevalence was highest in the age group 7-12 months, followed by the age groups 13-18 months and 19-24 months. The group 7-24 months accounted for 52 % of all diarrhoea cases among children under 5 years of age in the community. Forty-three per cent of the cases could be considered more severe (duration of diarrhoea at least 3 days with fever and vomiting) and 57 % milder.

*Hospital-based data (**VI**)*

The number of annual hospitalisations due to acute gastroenteritis in the period 1985 to 1995 varied from 2264 to 4663, and the mean number of annual hospitalisations in the study period was 3584. As the mean number of annual live births in Finland in the same period was about 65.000, approximately 5.6 % of all children born each year were hospitalised for acute gastroenteritis before reaching the age of 5 years. For 100.000 live births this would mean approximately 5500 hospital admissions due to acute diarrhoea each year in the age group 0-5 years. There was considerable variation between the years, no apparent trend to decrease, in fact a small increase over the years 1985 to 1995 (Figure 1/VI). The lowest number of hospitalisations was 2264 in 1988 and the highest 4663 in 1995. There was a higher incidence of admissions due to diarrhoea in winter and spring throughout the study period 1985-1995. In all years, there were few hospitalisations in August, September and October, the low season being from July to November. The high season started in December or January, peaked in March to May, and lasted to June or July (Figure 3/VI). During the study period approximately 52 % of diarrhoea admissions took place between January and April. The seasonality of hospital admissions in different age groups is shown in Figure 4/VI. The seasonal pattern was barely seen in the youngest infants aged 0 to 5 months, likewise in older children above the age of 48 months. The winter seasonality was most prominent in children aged 6 to 23 months. The mean duration of hospital stay for acute gastroenteritis shortened from 3.3 days in 1985 to 2.3 days by 1995. The six-monthly age distribution of children under the age of 5 years admitted for acute gastroenteritis is shown in Figure 2/VI. The hospitalisation rate was highest between 6 and 11 months of age, followed by 12 to 17 months and 18-23 months. The age group 6-23 months accounted for about 60 % of all hospitalisations for acute gastroenteritis among children between 0-5 years of age.

ROTAVIRUS INFECTIONS (**VI**)

Rotavirus detections in Finland in the 11-year study period varied from 653 to 1552 cases per year. The highest mean number of diagnoses (187 cases) was in the weeks 9-12, corresponding to March, the lowest (14 cases) in the weeks 37-40, corresponding to September (Figure 5/VI). In the 11 years of follow-up there was not a single 4-weekly period without detection of rotavirus at some site in Finland. Figure 6/VI shows the diagnoses of rotavirus infections in the laboratory of the Department of Virology, Haartman Institute, University of Helsinki. The seasonality of rotavirus infections corresponds to that of hospitalisations due to acute gastroenteritis, but the seasonal nature of rotavirus infections is much clearer. It may be surmised that other etiological agents, most likely viruses, explain some of the winter seasonality of acute gastroenteritis in Finland.

DEATHS FROM ACUTE GASTROENTERITIS (**VI**)

In the period 1986-1995 there were nine deaths due to acute gastroenteritis in otherwise healthy children under the age of 16 years in Finland. The ages of those succumbing were from 2 to 41 (mean 18) months; five children were female and four male. Six deaths occurred during the rotavirus season and three in the autumn. In two cases rotavirus was detected from the stools. One case yielded a stool culture positive for *Clostridium difficile.* Two children had negative stool cultures; in one of these the stools were also negative for rotavirus. In other cases no information was available on etiology. Four children died in 1991, other deaths being more evenly distributed (one in 1988 and 1989, two in 1992 and one in 1995). The deaths occurred in different parts of the country. The duration of the disease before admission ranged from 1 to 240 (mean 72) hours. Five children had already died at home or were moribund on arrival at hospital or health care center. Information on home treatment in hospital records was minimal. Two children had definitely received oral rehydration solution at home. Two children had severe electrolyte imbalance (blood sodium concentration 158 mmol/l on admission or a drop in blood sodium concentration from 146 mmol/l to 125 mmol/l in 12 hours), and one had intestinal bleeding. Other deaths were due to acute dehydration or were unexpected.

DISCUSSION

GLUCOSE CONCENTRATION AND OSMOLARITY OF ORS

Findings in experimental and animal tests have indicated that osmolarity rather than sodium concentration or the sodium-glucose ratio may be the most critical determinant of the efficacy of ORS (Sandhu et al. 1989, Farthing 1989, Elliot 1989b, Hunt et al. 1992, Cunha Ferreira et al. 1992); it would appear that optimal water absorption is obtained with a hypotonic solution with an osmolarity of 200-250 mosmol/l, a sodium concentration of 50-60 mmol/l and a glucose concentration of 50-100 mmol/l.

To follow up these recommendations and the earlier findings of Hirschhorn et al. (1968) and Sladen et al. (1969), a hypotonic ORS with a glucose concentration of 84 mmol/l, sodium of 60 mmol/l and osmolarity 224 mosmol/l was tested in an open trial in paediatric diarrhoea. This ORS performed better than the isotonic high glucose (144 mmol/l) ORS with the same sodium concentration then in use in Finland (**I**). The number of diarrhoeal stools, the duration of the diarrhoea episode and the consumption of maintenance fluid were smaller among recipients of the hypotonic solution. The open structure of the study ensured a large number of patients and results showing clear differences between groups. The results were confirmed in a double-blind randomised study (**II**). The number of patients here was smaller, but the results were similar. Stool output was reduced and consequently the consumption of maintenance fluid decreased significantly. A trend towards shorter duration of diarrhoea was also seen.

Similar superior absorption properties of reduced osmolarity ORS have been found in other clinical trials (Tables 9 and 10). Our results here are comparable with these findings. However, some differences may be noted. In a controlled trial in 60 Bangladeshi children aged 5-24 months Mahalanabis et al. (1995) observed that a hypotonic ORS (osmolarity 249 mosmol/l, sodium 67 mmol/l, glucose 89 mmol/l) performed better than the ORS-WHO in patients negative for rotavirus, whereas in patients positive for rotavirus it resulted in greater stool output than the ORS-WHO. We made a subgroup analysis for children positive and negative for rotavirus, and obtained contrasting results: the hypotonic ORS worked well in patients positive for rotavirus (**I-III**). This finding was confirmed in study **IV**, in which more than 90 % of patients were positive for rotavirus. In the study by Faruque et al. (1996a) 41 % of patients were positive for rotavirus, and the hypotonic ORS performed well in this subgroup. In other studies either the prevalence of rotavirus was not confirmed (El-Mougi et al. 1994, International Study Group 1995) or no separate analysis of rotavirus-positive patients was undertaken (Lentidoro et al. 1996, Shornikova et al. 1997).

Table 9 Characteristics of patients and comparison of oral rehydration solutions (ORS) in clinical trials with hypotonic ORS and ORS-WHO[1] or other standard ORS[2].

Study	Patients	Sample size	Glucose concentration (mmol/l)	Sodium concentration (mmol/l)	Solution osmolarity (mosmol/l)
Rautanen et al. 1993[2]	Acute diarrhoea Age 1-35 months	238	84	60	224
	Rota-positive subgroup	131	"	"	"
El-Mougi et al. 1994[1]	Acute diarrhoea Age 3-24 months	61	75	60	210
International Study Group 1995[1]	Age 1-24 months Acute diarrhoea	447	84	60	224
Mahalanabis et al. 1995[1]	Acute diarrhoea Age 5-24 months	60	89	67	249
	Rota-negative subgroup	35	"	"	"
Faruque et al.1996a[1] (sucrose)	Acute diarrhoea 41 % rota Age 6-30 months	46	58	60	257
Faruque et al.1996b[1]	Adult cholera	63	89	67	249
Santosham et al.1996[1]	Acute diarrhoea Age 1-24 months	190	75	75	245
Shornikova et al.1997[1]	Acute diarrhoea 28 % rota Age 1-36 months	123	84	60	224
Rautanen et al. 1997[2]	Acute diarrhoea Age 5-32 months	70	84	60	224
	Rota-positive subgroup	40	"	"	"

Table 10 Main results of clinical trials with hypotonic oral rehydration solution (ORS) and ORS-WHO[1] or other standard ORS[2] (ratio of means standard ORS / reduced osmolarity ORS).

Study	Stool output		ORS consumption		Duration
	At 24 hours	At 48 hours or total	At 24 hours	At 48 hours or total	of diarrhoea
Rautanen et al. 1993[2]	-	-	1.02 (rehydration)	1.27 * (maintenance)	1.31 **
rota-positive subgroup	-	-	1.06 (rehydration)	1.31 * (maintenance)	1.30 **
El Mougi et al. 1994[1]	1.50 **	-	1.2	-	1.5
International Study Group 1995[1]	1.32 **	1.39 **	1.15 **	1.18 **	1.22 **
Mahalanabis et al. 1995[1]	1.0	1.11	0.90	1.05	-
rota-negative subgroup	1.34	1.48 *	1.09	1.32 *	-
Faruque et al. 1996a[1] (sucrose)	1.46	1.42 *	1.20	1.11	-
Faruque et al. 1996b[1]	1.40 **	1.59 **	1.06	1.11	1.14
Santosham et al. 1996[1]	1.20	1.20	1.10 (rehydration)	1.40 (maintenance)	-
Shornikova et al. 1997[1]	-	-	0.97 (at 8 hours)	0.97	1.11
Rautanen et al. 1997[2]	-	-	0.99 (rehydration)	1.39 * (maintenance)	1.21
rota-positive subgroup	-	-	0.98	1.50 *	1.2

* $p \leq 0.05$

** $p < 0.01$

We further explored the lower limit of the glucose concentration and osmolarity by comparing a solution with an osmolarity of 204 mosmol/l (sodium concentration 60 mmol/l and glucose concentration 64 mmol/l) with the previously described hypotonic ORS (**IV**). The ultrahypotonic ORS performed well but no better than the 224 mmol/l ORS. There was no difference between the groups in the number of stools passed or amount of ORS consumed.

The patients receiving the ORS with an osmolarity of 224 mosmol/l seemed to gain more weight and recover faster from acidosis and their diarrhoea episode was shorter. These differences were not, however, significant. The lower limits of optimal glucose concentration and osmolarity of ORS probably need further investigation, but the present results suggest that a reduction of osmolarity from 224 mosmol/l does not significantly improve the performance of ORS.

In another study we compared two hypotonic ORS solutions of the same osmolarity (224 mosmol/l) with or without citrate (**III**). The glucose concentrations in the two solutions were different (84 mmol/l in that containing citrate and 64 mmol/l in that without citrate). The ORS containing citrate corrected acidosis faster, and during maintenance therapy the consumption of fluid was smaller in this group. This may reflect a faster correction of acidosis with earlier cessation of nausea and vomiting, subsequently promoting faster correction of dehydration; or alternatively it may result from more efficient water absorption due to better function of the glucose-enhanced sodium pump in patients receiving the solution with slightly higher glucose concentration. The latter hypothesis is in line with the findings in study **IV.**

Our first study was open and the nurses on the ward were aware of the type of ORS being used. After the study their impression was that the taste of the hypotonic ORS was more appealing to the children than that of the sweeter ORS in use in Finland. However, in none of our own or other clinical studies of hypotonic ORS has this point been objectively evaluated. Isolauri (1985a) compared a low-sodium (35 mmol/l) high glucose (200 mmol/l) ORS to the improved commercial ORS used in Finland (sodium 60 mmol/l, glucose 144 mmol/l), and it clearly emerged that children were unwilling to take the sweeter ORS and oral fluid therapy was significantly more often successful with the fluid with less sugar. Other studies have shown that the addition of flavouring does not enhance the acceptability of ORS. Probably as neutral a taste as possible is best. Thus, a further reduction in glucose concentration may reduce the problem of getting children to drink the solution.

In conclusion, the absorptive properties of an oral rehydration solution are increased if the glucose concentration is reduced close to 84 mmol/l. Further reduction may not help, although the question of the lower limit of glucose concentration has not been thoroughly investigated. The glucose concentration in the solution currently used in Finland was reduced from 144 mmol/l to 84 mmol/l in 1999.

WHO has been very cautious and resistant in making any changes to the composition of ORS. So far the only modification has been the replacement of bicarbonate by citrate. There has been much discussion on the optimal sodium content of ORS. Would 60 mmol/l of sodium be sufficient for cholera patients who can be rehydrated with oral fluids only, or should there be two different solutions for cholera and non-cholera diarrhoea. WHO has adhered to the single-solution policy. Now WHO is facing a new dilemma: should the glucose concentration and osmolarity of ORS be reduced.

Many studies have shown that the hypotonic ORS solution is superior to the current formula in non-cholera diarrhoea (Tables 9 and 10). The majority of diarrhoea cases in developing countries are non-cholera. Where cholera is present but not epidemic, it causes fewer than 5 % of all acute diarrhoea cases (WHO 1992b). More than 90 % of cholera cases are mild, and may be difficult to distinguish from other types of acute diarrhoeal disease (WHO 1992b). Even cholera cases can be successfully treated with a hypotonic solution (Faruque et al. 1996b). Less than 10 % of cases develop hyponatraemia. The question thus remains as to whether the isotonic ORS solution should be reserved for these cases and the majority be left to enjoy the benefits of hypotonic solution.

ROLE OF A BASE PRECURSOR IN ORS

The hypotonic ORS with and without a base precursor were both efficient for rehydration. However, the ORS containing the base precursor had clear advantages: total consumption was lower, the duration of vomiting shorter and acidosis corrected faster in this group. The reduced ORS consumption and faster cessation of vomiting may indeed be reflections of faster correction of acidosis. The fact that the duration of diarrhoea was not longer in those receiving ORS without a base precursor suggests that absorption of ORS was similar and not dependent on a base precursor. If the ORS without a base had not been absorbed, it would have induced osmotic diarrhoea and prolonged the episode.

As discussed above, the difference in glucose concentration between the two solutions may nonetheless play a role. The solution with the higher glucose concentration (and containing the base precursor) may have induced slightly better absorption of fluid and hence smaller consumption of ORS.

Our results are very similar to those in previous clinical studies by Clements et al. (1981), Islam et al. (1984b) and Elliott et al. (1988). Use of an ORS containing a base precursor is to be recommended. However, an ORS without a base or base precursor will correct dehydration, albeit more slowly. Sugar-salt solutions without base may be used as a substitute for ORS provided that the composition of SSS otherwise meets the criteria.

PROBIOTIC THERAPY IN ACUTE DIARRHOEA

The results here confirmed the previous findings of Isolauri et al. (1991), Kaila et al. (1992), Majamaa et al. (1995), Raza et al. (1995), Pant et al. (1996), Guarino et al. (1997) and Shornikova et al. (1997) demonstrating that administration of LGG shortens the duration of diarrhoea. The present study shows that to achieve maximal effect the LGG can and should be given as early as possible during rehydration. It would seem that one single early dose of LGG might be sufficient for desired effect; further doses during hospital stay did not improve the outcome. However, the sample sizes were small (11-19) in the different treatment groups (Table 6). Such a conception is supported by the findings of Goldin et al (1992) showing that LGG can colonise and survive in the human gastrointestinal tract for up to 7 days after ingestion.

Our study showed that LGG therapy and hypotonic ORS had a positive interaction in shortening the duration of diarrhoea. This could be explained by the biphasic nature of a rotavirus infection (Isolauri et al. 1994). The hypotonic ORS could reduce the early osmotic diarrhoea phase of a rotavirus infection while the LGG therapy could counteract the later phase caused by overgrowth of urease-producing bacteria.

HOME CASE MANAGEMENT PRACTICES IN PAEDIATRIC DIARRHOEA

As a general finding it can be said that home case management practices in paediatric diarrhoea in Finland have improved in the past 20 years, although no previous community-based data are available for direct comparison. The preadmission ORS use rate in admitted paediatric diarrhoea cases was 3 % in 1978, 29 % in 1987 (Isolauri et al. 1989), and 70 % in the present material, this constituting a significant improvement (Figure 17). However, in our present study the ORS use rate at home in all cases of diarrhoea in children under five was only 37 %. This low overall rate suggests that both health care personnel and parents need continuous education on ORT; it can be given in all diarrhoeas to prevent and correct dehydration. ORS packets could be introduced or even distributed to mothers at well-baby clinics to ensure unlimited access. Similar records of low ORS use rates are available from other developed countries. Conway et al. (1990) found that 31 % of paediatric diarrhoea cases in Leeds, England, had received ORS before admission to hospital. Snyder (1991) interviewed American paediatricians and found that less than 30 % would use an ORS which meets the AAP composition criteria.

ORS was significantly more often offered to children below the age of 24 months. This may reflect difficulties in persuading older children to drink the solution, or mothers' concern over the younger children. ORS was often (in 41 % of cases) diluted with other fluids, and in 38 % of cases this probably reduced the efficacy of the fluid, as mothers added extra water or sweet drinks. One fourth of ORS recipients were offered very small quantities of ORS. Parents appear to need more information on the proper use of ORS, adminitering it as such without mixing it with other, especially sweet drinks, and using it in proper quantities.

Increased fluid intake was well accepted by mothers, as 93 % of the children here were offered more fluids than normally during the diarrhoeal episode. However, the most common fluid primarily given for diarrhoea was water (56 %), which is far from optimal as it does not replace electrolytes and contains neither glucose nor energy. Use of soft drinks was low (10 %). In the United States use of nonphysiologic liquids like soft drinks in diarrhoea is suspected to be as high as 85-90 % (Snyder 1991). Use of homemade sugar-salt solutions was low (2 %). The risk of hypertonic dehydration may be increased when using homemade solutions if they are not properly mixed. SSS should not be recommended, at least not in conditions where standardised ORS packages are easily available.

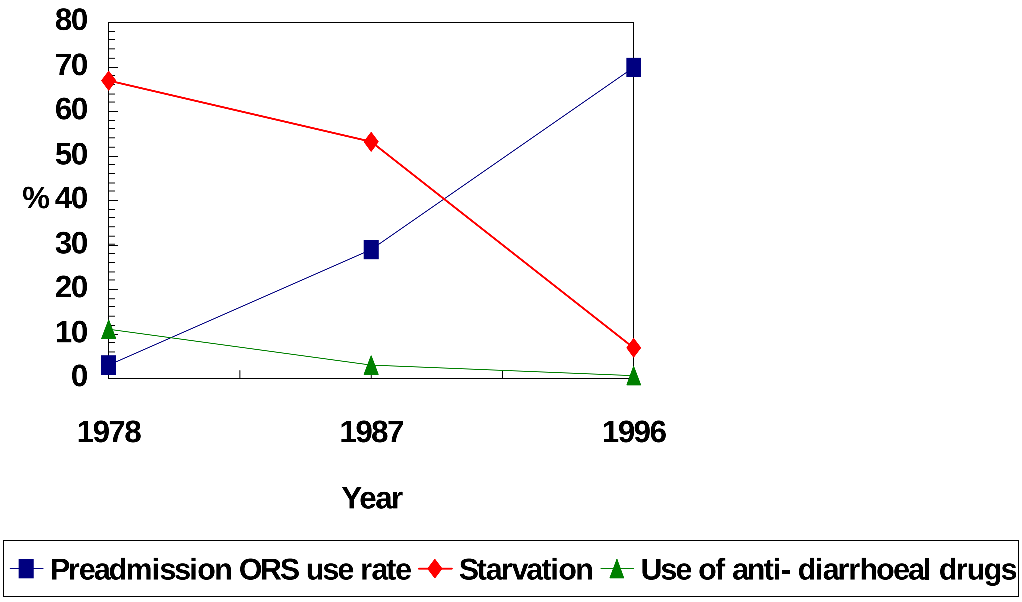


Figure 17 Improvement in home case management practices in paediatric diarrhoea in Finland in 1978 - 1996

Therapeutic starvation was a common practice in diarrhoea case management 20 years ago (Similä 1975). Isolauri et al. (1989) found that in 1978 67 % of admitted paediatric diarrhoea cases had been starved before admission. In 1987 this practice was adhered to in 53 % of cases. In our community-based data only 7 % of the children involved had fasted for at least one day, a significant improvement since 1987 (Figure 17); 55 % of the children received increased or normal amounts of food during the episode, and 63 % continued to receive normal-type food. Diet changes were mostly reasonable. Only 6 % of the children were put on a milk-free diet. According to recent studies there is no reason to withhold milk during uncomplicated diarrhoea (Dugdale et al. 1982, Isolauri et al. 1986, Chew et al. 1993, Brown et al. 1994), and this message has been well received among Finnish mothers. 74 % of the children who were breastfed at the time of onset were breastfed more frequently during the episode and the rest continued to receive normal amounts of breastmilk.

Use of antidiarrhoeal drugs in paediatric diarrhoea has not been a problem in Finland. In 1978 the rate of use before admission was as low as 11 %, and it continued to decrease to 3 % by 1987 (Isolauri et al. 1989). In our material the rate was only 0.7% (Figure 17). If drugs which are ineffective but harmless (e.g. medical carbon and dimethicon) are included, the rate of use was 2 %. In spite of this, continuous health education is needed, since two out of the three cases here receiving antidiarrhoeals had bought them abroad, where they are easily available and more frequently used than in Finland (Guandalini 1989, Goodburn et al. 1991, Costello et al. 1992, Haak et al. 1996).

Mothers and primary health care providers were well aware of the new findings showing that lactic acid bacteria products may shorten the duration of diarrhoea episodes (Isolauri et al. 1991, Majamaa et al. 1995). Use of these products was as high as 44 %, exceeding ORS use. Interestingly, mothers preferred to take these products in drug-like form (powder) instead of using food products containing lactic acid bacteria ("functional foods"). Our study results imply that lactic acid bacteria products should be taken as early as possible during the rehydration phase to achieve significant shortening of the duration of the disease. It is possible that a single dose early during rehydration is enough. However, our study did not evaluate the effect of LGG if given even earlier, before dehydration has developed. Advocation and possible provision of the first dose of lactic acid bacteria at health care centers and hospital emergency clinics could reduce the duration of diarrhoea and possibly the need for further visits or admission. A recent multicenter trial in ten European countries (Guandalini et al. 2000) concludes that administering ORS containing LGG to children with acute diarrhoea is safe and shortens the duration of diarrhoea.

More than two thirds of the diarrhoea episodes here were managed at home. If medical consultation was sought, the child was most often taken to the primary health care doctor.

These doctors and well-baby clinic nurses were also the most commonly used sources of information after relatives and friends when advice was asked. This emphasises the role of primary health care staff in providing proper advice. Eleven per cent of cases were taken to the hospital emergency clinic and 5 % were hospitalised. Children below the age of two years were significantly more often taken to hospital. Accordingly there would be approximately 3890 emergency visits and 1730 hospital admissions yearly due to diarrhoeal diseases for every 100.000 healthy children under the age of five in Finland, which would mean approximately 5500 annual admissions due to gastroenteritis in this age group in Finland. The reported admissions due to diarrhoea in this age group were 2878-4215 in the years 1986-1995. The study was conducted during the rotavirus peak season. Diarrhoea caused by rotavirus leads to dehydration and hospitalisation more often than diarrhoeas of other causes, which may explain the difference between the estimated and reported admissions.

CONSUMPTION OF ORS IN FINLAND

According to the Finnish Statistics on Medicines 1.38 million Finnish marks were spent on ORS in Finland in 1996, corresponding to 151 000 packages providing 500 ml of ORS. In 1996 the total number of children under five in Finland was 320 100. If the annual diarrhoea attack rate is 0.48 in this age group, this would mean 155 000 annual diarrhoeal episodes among under fives. Two packages of ORS given per episode would mean consumption of 310 000 packages of ORS in this age group alone. This confirms the estimate that the ORS use rate observed in the community-based study probably reflects the situation throughout Finland and ORS may be underused.

EPIDEMIOLOGY

Within 30 years from the 1940s there was a marked reduction in morbidity and mortality from acute diarrhoea in children in Finland. Since the 1980s morbidity has remained stable while mortality has continued to decrease. From the 1940s on the seasonal pattern changed from summer to winter and spring diarrhoea, most probably due to the reduction in and near disappearance of bacterial diarrhoea. The age distribution changed from very young infants to children aged 6-24 months. In the present material the seasonal pattern and the age distribution followed the pattern described by Vesikari et al. 1981, Mäki et al. 1983 and Isolauri et al 1989. In the community the diarrhoea prevalence was highest in the 7-12 months age group, and 52 % of all diarrhoea cases occurred in the age group of 7-24 months. The mean duration of a diarrhoea episode was rather long, 4.8 days. This is best borne in mind if a mother seeks advice early during the disease; she should be warned that most probably the disease will continue several days despite ORT.

The number of hospital admissions remained stable or increased slightly in the period 1985 to 1995, mean annual hospitalisations being 3584. The hospitalisation rate was highest in the age group of 6-11 months. Children aged 6-23 months accounted for 60 % of all hospitalisations. It is obvious that improved hygiene and case management are not further reducing morbidity in Finland. Similarly, the morbidity and number of hospitalisations due to diarrhoea in the United States have declined only slightly over the past 15 years (Glass et al. 1996). The magnitude of the disease burden entailed in rotavirus hospitalisations is assessed to be over one billion dollars yearly in the United States (Glass et al. 1996), which has focused the attention of investigators on the cost-effectiveness of rotavirus vaccination programmes.

In Finland, rotavirus is responsible for 25 % of all diarrhoea episodes and for 75 % of severe diarrhoea episodes in the community among children under three years of age (Ruuska et al. 1991). It is estimated that up to 60 % of hospitalised diarrhoea cases are due to rotavirus. With an effective rotavirus vaccine more than 90 % of severe rotavirus episodes and nearly 100 % of hospitalisations for rotavirus gastroenteritis could be avoided (Joensuu 1999).

Although morbidity remains stable, the duration of hospital stay due to diarrhoea was reduced by one day between 1985 and 1995. This reflects the efficacy of current case management using ORT in hospitals.

MORTALITY

Deaths from acute diarrhoea have become very rare in developed countries. In Finland the number of deaths from diarrhoea has fallen dramatically over the past decades, and in developed countries diarrhoeal deaths are considered avoidable. Similä pointed out in 1975 that every other diarrhoeal death occurs at home or on the way to hospital. Also in our present material more than half of the deaths in 1986-95 occurred at home or on the way to hospital. This stresses the importance of proper home case management and advice-seeking practices.

All nine deaths from diarrhoea in otherwise healthy children in Finland occurred in young children aged less than 4 years (all deaths from diarrhoea in children less than 16 years were searched). Findings in the United States have been similar, the 300 annual diarrhoeal deaths between 1985 and 1991 occurring mainly among children aged 3 to 24 months (Kilgore et al. 1995). This would indicate that the diarrhoeal diseases, especially rotavirus, are most dangerous in infants and young children and special attention should be addressed to the proper home management and hospitalisation of these children.

SUMMARY

The discovery of ORT has been considered one of the greatest therapeutic advances of this century. During the 1990s several investigators have expressed concern at the low use of this treatment mode in the developed world. Some criticism of it has focused on the composition of ORS, especially the optimal sodium content. In the late 1980s experimental studies showed that a reduction in glucose concentration and osmolarity of these solutions increased their efficacy. The latest development in the treatment of acute diarrhoea is the use of live microbial feed supplements (probiotics) which may promote intestinal health.

The present study was designed to investigate various compositions of ORS for use in Finland, with special interest in reduced glucose concentration and osmolarity and combined

use of ORT and probiotic therapy. It was also sought to form a picture of current home case management practices and the significance of acute paediatric diarrhoea in Finland.

In a search for an optimal glucose concentration and osmolarity for ORS 431 children aged 1 to 36 months suffering from acute gastroenteritis received either the isotonic ORS with a glucose concentration of 144 mmol/l and an osmolarity of 304 mosmol/l then used in Finland (170 patients), hypotonic ORS with a glucose concentration of 84 mmol/l and osmolarity 224 mosmol/l (197 patients) or an ultrahypotonic ORS with a glucose concentration of 64 mmol/l and osmolarity 204 mosmol/l (64 patients) (studies **I**, **II** and **IV)**. The hypotonic ORS was found to be the most effective, resulting in shorter duration of diarrhoea and hospital stay, fewer diarrhoeal stools in the hospital and reduced consumption of ORS during maintenance therapy in comparison with the standard ORS. This difference was also clearly seen among patients suffering from rotavirus diarrhoea. There were no differences between the two solutions with regard to weight gain, need for unscheduled intravenous therapy, electrolyte balance, recovery from acidosis or urine sodium excretion during hospital stay. It may be concluded that the absorptive properties of ORS are enhanced if the glucose concentration is reduced close to 84 mmol/l and osmolarity close to 224 mosmol/l. Further reduction of glucose concentration to 64 mmol/l was not seen here to improve absorption. In the comparison of the hypotonic with the ultrahypotonic ORS, consumption of ORS during maintenance, weight gain, number of diarrhoeal stools in the hospital, duration of diarrhoea in the hospital and recovery from acidosis were equal. The glucose concentration in the solution currently used in Finland has been reduced to 84 mmol/l in 1999.

Another 53 patients received hypotonic ORS without a base precursor (citrate) and 54 patients a similar solution with 10 mmol/l citrate, to establish whether the base precursor is essential in the composition of a hypotonic ORS (study **III)**. The patients receiving the hypotonic ORS with citrate recovered faster from acidosis and consumed less ORS. The duration of diarrhoea and the number of diarrhoeal stools in the hospital, weight gain and need for unscheduled intravenous therapy were no different between the groups. The results were similar in patients positive for rotavirus. However, in this group the duration of vomiting and hospital stay were significantly shorter in the citrate ORS group. Use of a base precursor is recommendable even in the hypotonic ORS, but in situations where these ingredients are not available due to limited resources or otherwise, use of an ORS without a base or base precursor may be considered adequate.

To investigate the influence of LGG therapy and to determine the optimal timing of its administration in relation to ORT, 93 patients received LGG (study **IV)**. Twenty-eight patients received one single dose at commencement of rehydration therapy and 33 continued to receive LGG twice a day throughout the hospital stay. Thirty-two patients received an initial dose of placebo and thereafter "late-onset LGG therapy", and 30 received placebo preparation throughout the study. LGG and hypotonic ORS both had an independent shortening effect on the duration of diarrhoea, and they also evinced significant interaction. The results suggest that one single early dose of LGG might suffice.

In order to study home case management practices and paediatric diarrhoea morbidity a community-based retrospective study was conducted at well-baby and maternity clinics in Espoo, where 1726 mothers with 2230 children under five years of age were interviewed. The two-week diarrhoea incidence among children under five was 3.7 % and the seasonally adjusted annual diarrhoea incidence rate was 0.48 episodes per child per year. The rate of increased fluid intake was 93 %. Overall ORS use rate at home was 37 %. Mothers had a tendency to mix the solutions with other fluids (41 %) and to give them in very small amounts. Fifty-five per cent of the children were offered normal or increased amounts of food during the episode, and 93 % were not fasted for diarrhoea. The antidiarrhoeal drug use rate was only 0.7 %. Lactic acid bacteria products were given in 44 % of cases. Home case management practices in paediatric diarrhoea have, it is true, much improved in the last 20 years, but the ORS use rate is still rather low and ORS is not optimally administered at home. The practice of starvation has been dramatically reduced, from 67 % in 1978 to 7 % in the present study, but should rather be abandoned altogether.

Diarrhoeal mortality in Finland has continued to decrease in the past 10 years. More than half of the diarrhoeal deaths involved here had occurred at home or on the way to hospital, which underlines the importance of proper home therapy and advice-seeking practices. The number of hospital admissions due to diarrhoea remained stable or possibly increased in the period 1985-1995. The duration of mean hospital stay due to diarrhoea was reduced by one day between 1985 and 1995, indicating the effectiveness of ORT and continuous feeding. However, improved case management and hygiene seem not to further reduce diarrhoeal morbidity in Finland. Other interventions such as rotavirus vaccination programmes are needed to reach this goal.

PRINCIPAL FINDINGS

Major results emerging from this study are: 1) reduction of glucose concentration and osmolarity of ORS (to approximately 224 mosmol/l) improves the rehydrating properties of the solution; 2) LGG therapy shortens the duration of a diarrhoeal episode when given early during the episode, possibly one early dose being enough; 3) home case management practices of paediatric diarrhoea have much improved during the last 20 years but the overall ORS use rate is still less than optimal; and 4) diarrhoeal mortality has continued to decrease but morbidity remained stable or increased in the period 1985-1995.

The results of this study and other similar findings led to the reduction of glucose concentration and osmolarity in the rehydration solution currently used in Finland in 1999. As suggested in this study, a recent multicenter European trial recommends use of hypotonic solutions and inclusion of LGG in the ORS to optimise the therapy of acute-onset diarrhoea in infants. Improved case management has reduced diarrhoeal mortality in Finland to very low levels. To reduce diarrhoeal morbidity other interventions such as rotavirus vaccination programmes are needed.

YHTEENVETO

Ripulitaudin aiheuttaman kuivuman hoidossa käytettävän oraalisen rehydraation keksimistä on pidetty eräänä suurimpana lääketieteellisenä keksintönä tällä vuosisadalla. 1990-luvulla monet tutkijat ovat olleet huolestuneita oraalisen rehydraation vähäisestä käytöstä kehittyneissä maissa. Oraalisen rehydraatioliuoksen (ORS) koostumus, erityisesti oikea natrium-pitoisuus, on herättänyt runsasta keskustelua. 1980-luvun lopulla useat kokeelliset tutkimukset osoittivat, että sokeripitoisuuden ja osmolariteetin lasku hypo-osmolaariseksi parantavat ripulijuoman nesteytysominaisuuksia. Uusin edistysaskel lasten ripulin hoidossa on probioottien käyttö. Nämä ovat eläviä mikro-organismeja, jotka lisäävät suoliston hyvinvointia.

Tutkimuksessa selvitettiin Suomeen soveltuvan oraalisen rehydraatioliuoksen optimaalista koostumusta, erityisesti sokeripitoisuutta ja osmolariteettia, sekä oraalisen rehydraation ja probioottihoidon yhteiskäyttöä. Tutkimuksessa pyrittiin myös selvittämään lasten ripulitaudin kotihoitokäytäntöjä sekä ripulitaudin merkittävyyttä lasten sairastuvuuden aiheuttajana Suomessa.

Ripulijuoman optimaalisen sokeripitoisuuden ja osmolariteetin selvittämiseksi kolmessa kliinisessä tutkimuksessa yhteensä 431 akuuttia ripulitautia sairastavaa 1-36 kuukauden ikäistä lasta sai joko isotonista (glukoosipitoisuus 144 mmol/l, osmolariteetti 304 mosmol/l, 170 potilasta), hypotonista (glukoosipitoisuus 84 mmol/l, osmolariteetti 224 mosmol/l, 197 potilasta) tai ultrahypotonista (glukoosipitoisuus 64 mmol/l, osmolariteetti 204 mosmol/l, 64 potilasta) oraalista rehydraatioliuosta. Hypotoninen ripulijuoma osoittautui tehokkaimmaksi lyhentäen ripulin kestoa 17-24 %:lla, vähentäen ripuliulosteiden lukumäärää 35-37 %:lla ja vähentäen ripulijuoman tarvetta 21-28 %:lla oraalisen nestehoidon ylläpitovaiheessa verrattuna isotoniseen liuokseen. Erot tulivat selvästi esiin myös potilailla, joilla oli rotaviruksen aiheuttama ripuli. Potilaiden elektrolyyttitasoissa, emäsvajeen korjautumisessa ja virtsan natriumerityksessä ei ollut eroja liuosten välillä. Sokeripitoisuuden alentaminen 64 mmol/l:iin (ultrahypotoninen liuos) ei enää lisännyt imeytymistä. Hypotonisen ja ultrahypotonisen ORS-ripulijuoman kulutus ylläpitohoidon aikana oli verrannollista, samoin painonnousu, ripuliulosteiden määrä, ripulin kesto ja emäsvajeen korjautuminen. Tuloksista voidaan päätellä, että oraalisen rehydraatioliuoksen nesteytysominaisuudet paranevat mikäli sokeripitoisuutta vähennetään lähelle tasoa 84 mmol/l ja osmolariteettia lähelle 224 mosmol/l. Suomessa tällä hetkellä käytössä olevan ripulijuoman glukoosipitoisuus alennettiin tasolta 144 mmol/l tasolle 84 mmol/l keväällä 1999.

Ripulijuoman emäslisän tarpeellisuuden selvittämiseksi 53 potilasta sai hypotonista ripulijuomaa ilman emäslisää (sitraattia) ja 54 potilasta sai vastaavaa liuosta, johon oli lisätty 10 mmol/l sitraattia (emäsprekursori). Potilaat, jotka saivat hypotonista ripulijuomaa johon oli lisätty sitraattia, korjasivat nopeammin emäsvajeensa ja kuluttivat vähemmän ripulijuomaa. Ripulin kestossa sairaalassa, ripuliulosteiden lukumäärässä sairaalassa, painonnousussa ja suunnittelemattoman suonensisäisen nesteytyksen tarpeessa ei ollut eroja ryhmien välillä. Tulokset olivat vastaavia rotaviruspositiivisilla potilailla, joskin tässä potilasryhmässä oksentelutaipumuksen kesto ja sairaalassolo olivat merkitsevästi lyhempiä sitraatti-ORS ryhmässä. Emäslisä on siten hyödyllinen myös hypotonisessa ripulijuomassa. Emäksetöntä ripulijuomaa voidaan käyttää korvikkeena, jos muiden ainesosien määrä on oikeissa rajoissa.

Oraalisen nestehoidon ja maitohappobakteerivalmisteen (LGG) yhteisvaikutusten ja LGG-hoidon optimaalisen ajoituksen selvittämiseksi 93 potilasta sai LGG-hoidon. 28 potilasta sai yhden ainoan annoksen nesteytyksen alussa ja 33 potilasta sai LGG-valmistetta kahdesti päivässä koko sairaalassaoloajan. 32 potilasta sai nesteytyksen alussa lumevalmistetta ja vasta sen jälkeen "myöhäisen LGG-hoidon". 30 potilasta sai lumevalmistetta koko tutkimuksen ajan. LGG ja hypotoninen ripulijuoma lyhensivät kumpikin itsenäisesti ripulin kestoa. Hoidoilla oli myös merkittävä yhteisvaikutus. Tulokset viittaavat siihen, että yksi LGG-annos oraalisen nestehoidon alussa on riittävä.

Espoolaisissa lasten- ja äitiysneuvoloissa suoritettiin takautuva väestöpohjainen kyselytutkimus lasten ripulin kotihoitokäytäntöjen ja ripuliin sairastuvuuden selvittämiseksi. 1726 äitiä ja heidän 2230 alle 5-vuotiasta lastaan haastateltiin. Kahden viikon ripulisairastuvuus tässä ikäryhmässä oli 3.7 % ja vuotuinen kausittaisen vaihtelun huomioiva sairastuvuus oli 0.48 ripuliepisodia lasta kohti. 93 %:lle lapsista tarjottiin ripulin aikana tavallista runsaammin nesteitä. ORS:ia tarjottiin kotihoidossa 37 %:lle lapsista. Äidit sekoittivat useasti (41 %) ORS:iin muita nesteitä huonontaen siten ripulijuoman nesteytysominaisuuksia, ja/tai antoivat liuosta hyvin pieniä määriä. 55 %:lle lapsista tarjottiin normaali tai tavallista suurempi määrä ruokaa ripulin aikana, ja vain seitsemää prosenttia lapsista paastotettiin vähintään yhden vuorokauden ajan. Ripulilääkkeiden käyttö oli vähäistä (0.7 %). Maitohappobakteerivalmisteita annettiin 44 %:lle potilaista. Lasten ripulin kotihoitokäytännöt ovat selvästi parantuneet 20 viime vuoden aikana. Aikaisempaa väestöpohjaista ripulijuoman käyttöprosenttia ei ole tiedossa vertailua varten, mutta ilmeisimminkin ripulijuoman käyttö Suomessa on lisääntynyt, koska vuonna 1978 sairaalaan otetuista ripulilapsista vain 3 % oli saanut kotona ripulijuomaa verrattuna 70 %:iin tässä tutkimuksessa. Paastottaminen on jyrkästi vähentynyt 67 %:n tasolta vuonna 1978 seitsemään prosenttiin nykyisessä tutkimuksessa, mutta keskeytymättömään ruokintaan tulisi pyrkiä aina.

Ripuliin kuolleisuus Suomessa on edelleen vähentynyt viimeisen 10 vuoden aikana. Yli puolet kuolemista tapahtuivat kotona tai matkalla sairaalaan, korostaen tehokkaan kotihoidon ja oikein ajoitetun hoitoon hakeutumisen tärkeyttä. Ripulista johtuvat sairaalahoidot ovat pysyneet ennallaan tai mahdollisesti hieman lisääntyneet vuosina 1985-1995. Keskimääräinen ripulin hoitoaika sairaalassa on samalla aikavälillä lyhentynyt vuorokaudella osoituksena oraalisen nestehoidon ja keskeytymättömän ruokinnan tehokkuudesta tai heijastaen mahdollisesti sairaaloiden tiukentuneita talousarvioita. Tehostunut ripulin hoito ja parantunut yleinen hygieniataso eivät enää vähennä ripuliin sairastuvuutta Suomessa. Tämän päämäärän saavuttamiseksi tarvitaan muita toimenpiteitä, kuten esimerkiksi rotavirusrokotteen liittäminen rokotusohjelmaan.

TÄRKEIMMÄT JOHTOPÄÄTÖKSET

Tärkeimmät tutkimuksen perusteella tehtävät johtopäätökset ovat: 1) oraalisen rehydraatioliuoksen nesteytysominaisuudet paranevat sokeripitoisuuden ja osmolariteetin vähentämisellä (noin tasolle 224 mosmol/l); 2) LGG-hoito nestehoidon alussa lyhentää ripulin kestoa, mahdollisesti kerta-annos LGG:tä on riittävä; 3) lasten ripulin kotihoitokäytännöt ovat selvästi parantuneet 20 viime vuoden aikana, mutta ripulijuoman käyttöaste ei ole vieläkään optimaalisella tasolla; sekä 4) ripulikuolleisuus Suomessa on edelleen vähentynyt, mutta ripulitautisairastuvuus on pysynyt ennallaan tai mahdollisesti hieman lisääntynyt vuosina 1985-1995.

Tämän ja muiden samanaikaisten tutkimusten tulokset johtivat Suomessa tällä hetkellä käytössä olevan ripulijuoman glukoosipitoisuuden ja osmolariteetin alentamiseen keväällä 1999. Kuten oma tutkimuksemme, myös tuore eurooppalainen monikeskustutkimus suosittaa hypotonisen ripulijuoman käyttöä ja suosittaa myös LGG:n lisäämistä juomaan.

Parantuneet hoitokäytännöt ovat vähentäneet ripulikuolleisuuden Suomessa hyvin alhaiseksi. Ripulitautisairastuvuuden vähentämiseksi tarvitaan muita toimenpiteitä, kuten esimerkiksi rotavirusrokotteen liittäminen rokotusohjelmaan.

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