Evidence of a dominant role for low osmolality in the efficacy of cereal based oral rehydration solutions: studies in a model of secretory diarrhoea

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Abstract

Clinical trials suggest that including naturally occurring complex carbohydrate in oral rehydration solutions (ORS) in place of glucose increases water absorption and reduces stool volume during acute diarrhoea. The mechanisms for this greater clinical efficacy has not been established. This study examined the ability of two hypotonic rice based ORS, RS-ORS (137 mOsm/kg) and RP-ORS (143 mOsm/kg), and HYPO-ORS (240 mOsm/kg) a glucose equivalent ORS, to effect water absorption by in vivo perfusion of normal and secreting rat small intestine. The results were compared with those for two widely used conventional hypertonic ORS, WHO-ORS (331 mOsm/kg) and UK-ORS (310 mOsm/kg). In the normal intestine, water absorption was similar from WHO-ORS (87.4 (45.1-124.6) μ l/min/g; median and inter-quartile range) and UK-ORS (57.6 (41.5-87)) but less than from the hypotonic solutions ($p < 0.02$); water absorption from RS-ORS (181.8 (168.5-193.8)) and RP-ORS (195.7 (179.3-207.9)) was similar but less than from HYPO-ORS (241.3 (230.6-279.7); $p < 0.005$). In the secreting intestine, all ORS reversed net secretion of fluid to net absorption; the hypotonic solutions, HYPO-ORS (105.2 (95.2-111)), RS-ORS (127.7 (118.3-169.4)) and RP-ORS (133.7 (122.1-174.5)), produced more water absorption ($p < 0.005$) than the hypertonic solutions WHO-ORS (47.1 (29-75.9)) and UK-ORS (24.9 (18.4-29.4)). The rice based solutions promoted most water absorption in secreting intestine ($p < 0.007$). These data indicate that low osmolality is of primary importance in mediating the increased water absorption from cereal based ORS.

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Acute infectious diarrhoea continues to be a major cause of morbidity throughout the world,

particularly in preschool children, with an unacceptable mortality in this age group approaching 4 million each year.¹ Rehydration with oral rehydration solutions (ORS) containing monomeric glucose as substrate has been considered the most important therapeutic breakthrough of this century.² Although highly effective for rapid rehydration when given by mouth, standard glucose electrolyte ORS do not reduce the volume or duration of the diarrhoea³ and may actually increase stool volumes. This can discourage the mother or other attendant who administers ORS⁴ and compromise the rehydration process. Several clinical trials with cereal based ORS⁵⁻¹⁴ have shown dramatic improvements over conventional glucose electrolyte oral rehydration treatment with reduced duration and severity of diarrhoea and an associated reduction in the volume of ORS required for rehydration. The reasons why cereal based ORS have been so successful has not been examined but a number of possible mechanisms have been proposed including increased substrate availability without increased osmolality,⁴ kinetic advantage of oligosaccharides over glucose monomers,^{15 16} and low osmolality.¹⁷⁻²⁰

To explore these possible mechanisms further we studied the ability of hypotonic cereal based ORS and a glucose equivalent monomeric ORS to effect water and electrolyte absorption in an animal model and compared these findings with two widely used conventional glucose-electrolyte ORS.

Materials and methods

ORAL REHYDRATION SOLUTIONS STUDIED

Table I shows the composition of the ORS perfused. We used two conventional standard ORS - namely, the World Health Organisation ORS (WHO-ORS) and the ORS formulation recommended in the British Pharmacopoeia (UK-ORS), which until recently was the most widely used ORS in the United Kingdom. A hypotonic ORS (HYPO-ORS) has been previously studied by our group¹⁹ and is now recommended by the European Society for Paediatric Gastroenterology and Nutrition²¹ as being the optimal formulation for European children. Rice starch (Sigma Chemical Co) and rice powder (local supermarket) ORS were prepared with an identical electrolyte composition and glucose content (after complete hydrolysis) to HYPO-ORS. Thus we were able to examine the effects of presenting the intestine with a similar glucose load but in monomeric or polymeric form with an obligatory reduction in

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TABLE I Composition of oral rehydration solutions perfused

Solute (mmol/l)	WHO-ORS	UK-ORS	HYPO-ORS	RS-ORS	RP-ORS	PES
Sodium	90	35	60	60	60	140
Potassium	20	20	20	20	20	4
Chloride	80	35	60	60	60	104
Bicarbonate	30	20	-	-	-	40
Citrate	-	-	10	10	10	-
Glucose	111	200	90	-	-	-
Rice starch/powder (g)	-	-	-	16.3*	17.4*	-
Osmolality (mOsm/kg)	331	310	240	137	143	288

*Yield 90 mmol/l glucose after complete hydrolysis.

WHO=World Health Organisation; UK=United Kingdom; HYPO=hypotonic; RS=rice starch; RP=ground rice powder; PES=plasma electrolyte solution; ORS=oral rehydration solutions.

Figure 1: Net water movement in normal rat small intestine. Data are presented as median and interquartile range. *WHO-ORS similar to UK-ORS but less than HYPO-ORS, RP-ORS, and RS-ORS; $p < 0.02$; **HYPO-ORS greater than RP-ORS and RS-ORS; $p < 0.005$.

osmolality accompanying the last. Comparison was also possible with the standard United Kingdom and developing world ORS.

INTESTINAL PERFUSION OF NORMAL AND SECRETING RAT SMALL INTESTINE

Adult male Wistar rats (180–240 g) were fasted for 18 hours with free access to water. Anaesthesia was induced by intraperitoneal injection of sodium pentobarbitone (60 mg/kg) and maintained as necessary by interval intramuscular injection (30 mg/kg). Body temperature was measured with rectal thermometer and maintained with an underlying heat pad. After laparotomy cannulae were inserted proximally by duodenotomy and distally by terminal ileotomy as described previously.^{22,23} Gentle lavage with warm isotonic saline (37°C) and air was used to clear the entire small intestine of residual contents before instilling 75 µg of cholera toxin²² in

Figure 2: Net water movement in secreting rat small intestine. Data are presented as median and interquartile range. *RP-ORS, RS-ORS, and HYPO-ORS all greater than WHO-ORS; $p < 0.005$; **HYPO-ORS less than RP-ORS and RS-ORS; $p < 0.007$.

5 ml of isotonic saline for two hours to induce a stable secretory state.²⁴ For experiments with normal intestine, 5 ml of plasma electrolyte solution (PES) were instilled in place of cholera toxin. The small intestine was then perfused with either PES or an ORS at 0.5 ml/min for one hour to ensure steady state conditions, after which three successive 10 minute collections of effluent were made from the distal cannula. At the end of the experiment the rats were killed by intracardiac injection of sodium pentobarbitone and exsanguination. The perfused segment of entire small intestine was removed, rinsed, blotted, and desiccated at 100°C to obtain the dry weight.

Mean marker recovery for 66 perfusions, comprising three consecutive 10 minute collections each, was 102.1 (SEM 1.48)%. The percentage variation around the mean for [¹⁴C]-PEG concentrations was 2.6 (0.2)% confirming that steady state conditions were indeed obtained. Each solution was perfused in eight to 10 rats with normal and with secreting intestine.

HYDROLYSIS OF RICE POWDER AND RICE STARCH

Acid hydrolysis²⁵ was performed wherein samples of effluent were incubated with hydrochloric acid (1.0 mol/l) for two hours at 100°C. At the end of the reaction sodium hydroxide (1.0 mol/l) was added to neutralise the sample before glucose analysis. This method was effective at producing complete carbohydrate hydrolysis within two hours and was validated in preliminary experiments against an enzymatic method.¹⁶

PERFUSATE ANALYSIS

Sodium and potassium concentrations were analysed with flame photometry (Instrument Laboratories 943), chloride concentration by Chemlab CCM chloride meter, bicarbonate concentration by Corning CO₂ and glucose concentration by Beckman Glucose Analyser 2. Osmolality was analysed with the vapour pressure technique with a Wescor 5500 osmometer. [¹⁴C]-PEG concentrations were measured in triplicate by liquid scintillation spectroscopy in an LKB Wallac ultra-beta 1219 scintillation counter.

CALCULATIONS

Net solute and water movements were calculated by standard formulae²⁶ from the measured solute concentration and [¹⁴C]-PEG counts in perfusate and effluent. The differences in transport data were analysed with the Wilcoxon rank test. All results were expressed as median and interquartile range. Two tailed tests were used throughout.

Results

WATER ABSORPTION

In normal intestine (Fig 1) water absorption was similar from WHO-ORS and UK-ORS but less than from HYPO-ORS and the rice based solu-

Figure 3: Net glucose movement in normal rat small intestine. Data are presented as median and interquartile range. *UK-ORS greater than RP-ORS, RS-ORS, and WHO-ORS; $p < 0.002$; **HYPO-ORS greater than RP-ORS, RS-ORS, and WHO-ORS; $p < 0.002$.

tions ($p < 0.02$). Water absorption was similar from RS-ORS and RP-ORS but despite having the same total glucose content, HYPO-ORS produced more water absorption than the rice based solutions ($p < 0.005$).

In secreting intestine (Fig 2) all the solutions reversed net secretion to net absorption but all three hypotonic ORS promoted more water absorption than WHO-ORS and UK-ORS ($p < 0.005$). RS-ORS and RP-ORS promoted more water absorption in secreting intestine than did the hypotonic glucose monomer solution, HYPO-ORS ($p < 0.007$). Water absorption from rice based solutions in the secretory state was about 70% of that in the normal state compared with about 50% for all other ORS.

GLUCOSE ABSORPTION

In normal intestine glucose absorption (Fig 3) was greatest from UK-ORS and HYPO-ORS

Figure 4: Net glucose movement in secreting rat small intestine. Data are presented as median and interquartile range. *WHO-ORS greater than RS-ORS and HYPO-ORS; $p < 0.004$; **RP-ORS greater than HYPO-ORS; $p = 0.03$.

there being no significant difference between these solutions. Glucose absorption from RS-ORS was less than from HYPO-ORS and RP-ORS ($p < 0.002$) and of these, HYPO-ORS led to more glucose absorption than RP-ORS ($p = 0.002$).

In the secretory state glucose absorption (Fig 4) from UK-ORS was not different from all the other ORS despite the very low water absorption. Similar glucose absorption was obtained from WHO-ORS, UK-ORS, and RP-ORS. Glucose absorption from HYPO-ORS and RS-ORS was almost identical and was less from either than from WHO-ORS ($p < 0.004$). Glucose absorption from HYPO-ORS was less than from RP-ORS and WHO-ORS ($p = 0.03$).

SODIUM ABSORPTION

In normal intestine sodium absorption occurred from all the solutions (Fig 5) except for the low sodium UK-ORS ($p < 0.002$). Sodium absorption from the rice-based solutions was similar but significantly less than sodium absorption from HYPO-ORS and WHO-ORS ($p < 0.01$). None of the ORS perfused were able to reverse the net secretory state for sodium induced by cholera toxin (Fig 6); sodium secretion was greater with UK-ORS ($p < 0.002$).

CHLORIDE ABSORPTION

Table II summarises the data for net chloride movement. In normal intestine all ORS were associated with net chloride absorption but the highest chloride absorption was from HYPO-ORS ($p < 0.001$). UK-ORS, which had the lowest chloride concentration, was associated with least chloride absorption ($p < 0.02$). In secreting intestine UK-ORS led to chloride secretion ($p < 0.001$) whereas the other ORS still led to net chloride absorption albeit much lower than in normal intestine.

RELATIONS BETWEEN WATER AND SOLUTE UPTAKE

Tables III and IV summarise the data for individual and total solute movement in relation to net water movement. As expected there was direct correlation between total net solute absorption and net water absorption both in normal ($r = 0.76$, $p < 0.001$) and secreting intestine ($r = 0.77$, $p < 0.001$).

Discussion

All of the hypotonic ORS, whether they contained monomeric or polymeric carbohydrate as substrate, promoted more water absorption than the widely used hypertonic ORS and this accords well with the findings of other workers, both in human jejunum¹⁹ and in animal models.²²⁻²⁷ Both of the hypertonic ORS contained higher glucose concentrations and higher water absorption might have been expected from these solutions because of a greater stimulatory effect on active glucose transport. It is known, however, that a glucose concentration of 56 mmol/l²⁶ can exert a maximal stimulatory effect on water absorption and concentrations as low as 30 mmol/l, at least

Figure 5: Net sodium movement in normal rat small intestine. Data are presented as median and interquartile range. *UK-ORS less than all the other ORS; $p < 0.002$; **WHO-ORS and HYPO-ORS greater than RP-ORS and RS-ORS; $p < 0.01$.

in short segments of human jejunum, can promote sodium absorption.²⁸ Furthermore, restricting intraluminal sodium concentration in jejunal perfusion does not seem to limit glucose absorption.²⁹ It is extremely unlikely therefore that the profound differences in water absorption between the hypertonic and hypotonic ORS are related to differences in sodium or glucose concentration. The ORS containing complex carbohydrate led to increased water absorption in secreting intestine compared with the hypotonic monomer solution HYPO-ORS. It would seem therefore that low osmolality is the dominant factor rather than glucose transport when it comes to promoting net water absorption and this contention is supported by the higher water absorption from the WHO-ORS compared with UK-ORS in secreting intestine, despite their similar glucose absorption. In human jejunum there is an inverse relation between water absorption and perfusate osmolality³⁰ but below 250 mOsm/kg this inverse relation seems to disintegrate.³¹

Figure 6: Net sodium movement in secreting rat small intestine. Data are presented as median and interquartile range. *UK-ORS less than all other ORS; $p < 0.002$.

Although solute dependent sodium absorption via the cotransport mechanism is of major therapeutic importance during diarrhoeal states, sodium is mainly absorbed from the jejunum through other passive processes such as electro-neutral sodium chloride absorption and solvent drag.³⁰ According to data from animal perfusion systems, net sodium movement even in glucose containing solutions is linearly related to sodium concentration of the perfusate and this pertains equally in secreting intestine,^{22,24} although the threshold at which sodium absorption occurs is higher in the secretory state (120 mmol/l *v* 60 mmol/l). This linear relation has been confirmed with *in vivo* perfusion studies of human jejunum³² where net absorption of sodium from isotonic enteral feeds containing glucose polymer occurred only when the sodium concentration was above 80–90 mmol/l. It is not surprising therefore, that UK-ORS with its relatively low sodium concentration of 35 mmol/l did not promote net sodium absorption even in normal intestine, or that none of the solutions were able to reverse net sodium secretion to absorption in secreting intestine. In normal intestine the pattern of sodium absorption paralleled that for water absorption emphasising the importance of passive sodium absorption and solvent drag. These mechanisms were not able to offset the net sodium secretion induced by CT, however, which occurred despite net water absorption. In the whole gut of course, the reduction of this net sodium secretion by colonic salvage should be considered.

Glucose absorption from the hypotonic, monomeric, or polymeric ORS, paralleled water absorption whether the intestine was in a normal or secretory state. Exactly how glucose is absorbed from the jejunum remains undecided. Although saturation kinetics for glucose absorption from human jejunum have been shown^{33,34} suggesting that there is only active glucose transport, there is other evidence suggesting the participation of passive glucose absorption as well.³⁵ Indeed recent work in a perfusion system with rat jejunum has added to the probability of there being substantial passive glucose absorption after changes in the intercellular junctions once active electrogenic sodium absorption is stimulated.³⁶ Glucose absorption was highest in normal intestine from UK-ORS but not in secreting intestine and this certainly suggests an important role for passive glucose absorption due to solvent drag.

Rice starch is not a pure carbohydrate and on ignition about 0.4% remains as residue. Some of this will consist of protein. Amino acid stimulated sodium absorption occurs independently of hexose stimulated sodium absorption via a separate nutrient-sodium cotransporter. There would therefore be an additive effect on the passive water absorption that occurs secondary to solute absorption. In our deliberations we have discounted that as a significant factor because of the negligible fraction of rice starch and rice powder that is not carbohydrate. Of course in the rice solutions used in the published field trials the protein content may have been as high as 10% and may therefore have contributed more to secondary salt and water absorption.

TABLE II Net chloride movement in normal and secreting intestine

Solution perfused	Normal intestine. Mean (SEM) chloride movement (mmol/g/min)	Secreting intestine. Mean (SEM) chloride movement (mmol/g/min)
PES	0.24 (0.18)	-2.42 (0.51)
WHO-ORS	7.39 (0.83)	3.34 (1.61)
UK-ORS	1.16 (0.65)	-3.62 (0.33)
HYPO-ORS	11.17 (0.94)	1.0 (0.67)
RS-ORS	6.26 (0.47)	1.87 (0.58)
RP-ORS	7.51 (0.42)	3.09 (0.84)

Abbreviations as in Table I.

The exact relation between net water uptake and osmolality is not entirely clear from our findings. Similarly no strong relations can be drawn from these data between osmolality and the glucose and electrolyte uptakes. There are some variables that confound adequate dissection of the potential interrelations. Firstly, the sodium and other electrolyte concentrations were not uniform among the ORS. Further studies with a defined glucose polymer where electrolyte composition is constant but osmolality and substrate concentration is varied with a range of monomer and polymer concentrations may lead to a better understanding of these phenomena.

Although it is not absolutely certain whether these findings from our animal model will be relevant in human beings, the close parallelism in the handling of ORS in both rat and human perfusion models³⁷ is very encouraging. We believe that these findings suggest that osmolality is the key determinant of water absorption in both normal and secreting intestine and that it seems to be of particular importance in the secretory state. The success of complex carbohydrate containing ORS in clinical studies may be more closely related therefore to their very low osmolality relative to standard hypertonic monomer ORS than to the kinetic advantage factor or the increased substrate availability for glucose/sodium cotransport. Many field studies have used much higher loads of carbohydrate than we have because their main rationale was

the ability to greatly increase available substrate without incurring a substantial osmotic penalty. Their goal was not necessarily to keep the resulting ORS hypotonic. Our solutions containing rice derived glucose polymer promoted the highest water absorption in the secretory state but it is not known whether increasing the polymer concentration (but maintaining ORS hypotonicity) would enhance water absorption by further stimulating active glucose transport or whether water absorption would be jeopardised, even by a moderate increase in osmolality. The optimum polymer concentration therefore that would yield the best compromise between total glucose availability and low osmolality remains to be determined.

The standard hypertonic UK-ORS has already been replaced³⁸ by the hypotonic monomer solution HYPO-ORS in the British National Formulary but the World Health Organisation understandably remains cautious about modifying what has been a highly successful and very widely tested remedy. Substantial changes recommending the widespread use of hypotonic ORS containing monomeric or polymeric glucose (defined glucose polymer or crude complex carbohydrate) would require more evidence of clinical benefit after rigorous controlled clinical trials.

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TABLE III Total solute and water movement in normal intestine

Solutions perfused	Net water movement (μg/g/min)	Net glucose movement (mmol/g/min)	Net sodium movement (mmol/g/min)	Net potassium movement (mmol/g/min)	Net chloride movement (mmol/g/min)	Net total electrolyte movement (mmol/g/min)	Net total solute movement (mmol/g/min)
PES	2.6	-	1.4	-0.04	0.24	1.64	1.64
WHO-ORS	88.50	18.97	5.53	3.63	7.39	16.55	35.52
UK-ORS	63.87	32.96	-1.97	0.93	6.66	3.76	36.72
HYPO-ORS	250.78	30.13	6.04	5.26	11.17	22.59	52.72
RS-ORS	182.39	14.01	2.94	4.36	6.26	13.68	27.69
RP-ORS	195.3	22.49	3.5	5.03	7.62	16.24	38.73

Abbreviations as in Table I.

TABLE IV Total solute and water movement in secreting intestine

Solutions perfused	Net water movement (μg/g/min)	Net glucose movement (mmol/g/min)	Net sodium movement (mmol/g/min)	Net potassium movement (mmol/g/min)	Net chloride movement (mmol/g/min)	Net total electrolyte movement (mmol/g/min)	Net total solute movement (mmol/g/min)
PES	-53.19	-	-4.96	-0.94	-2.4	-8.32	-8.32
WHO-ORS	52.78	25.54	-5.86	2.21	3.34	-0.31	25.23
UK-ORS	23.87	18.64	-9.48	3.36	-3.62	-9.74	8.9
HYPO-ORS	105.1	16.07	-4.17	2.69	1.01	-0.25	15.82
RS-ORS	138.32	15.87	-3.26	2.8	1.87	1.61	17.48
RP-ORS	145.46	19.01	-2.51	3.8	3.09	4.51	23.52

Abbreviations as in Table I.

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