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Hydralyte: Mechanism and speed of uptake to treat dehydration		14 August 2017 Revised 28 May 2019

Summary

Prevention and treatment of dehydration in patients involves absorption of water and electrolytes from the small intestine into the bloodstream. The key to effective absorption is the coupled transport of glucose and sodium molecules, which occurs at the intestinal surface. Glucose stimulates sodium uptake, and water absorption follows. The absorption of potassium, chloride and citrate occurs simultaneously with sodium transport.

Potassium appears to be absorbed by a "solvent drag mechanism" i.e. it is pulled along with water. Citrate and chloride are absorbed to maintain charge balance across cell membranes.

The concentration of glucose and electrolytes in Hydralyte ORS is optimal for rapid and effective hydration and electrolyte replacement.

There has been no clinical research specifically looking at the uptake kinetics of Hydralyte or a directly equivalent ORS. However, inferences can be drawn from studies with other model beverages.

Several studies have applied perfusion tube techniques to estimate water and solute absorption. Different segments of the small intestine, where absorption takes place, have been examined. It's been discovered that water uptake varies considerably, according to both the beverage solution and the intestinal region. Water alone is most rapidly absorbed in the duodenum (first 25 cm section) whereas sugar-electrolyte solutions promote faster water absorption in the proximal jejunum (25 to 50 cm).

Possibly the most reliable method to evaluate overall fluid uptake rate has involved use of radiolabelled water (deuterium H_2O) in the consumed beverage. In a 2009 study of this type, mildly dehydrated adults consumed a 600 ml dose of a "Hydralyte-like" solution containing 20 mmol/L sodium chloride and 3% glucose. About 50% of the fluid (300 ml) was delivered to the blood stream in 9 minutes, whereas the majority was delivered by 30 minutes (Jeukendrup et al 2009).

A parameter, t ½, was defined as a measure of water uptake, representing the time taken from beverage consumption until the radio-labelled water reached 50% of its maximum concentration in the bloodstream.

The glucose-electrolyte solution most closely resembling Hydralyte was hypotonic and contained 3% glucose and 20 mmol/L sodium chloride. t ½ occurred in 10.3 minutes, whereas the solution most similar to water (no glucose) took 13 minutes, and the 6% glucose solution, (similar to a sports drink) took 16 minutes. On this basis, overall water uptake from the hypotonic ORS was about +25% faster than water alone, and +50% faster than a high sugar "sports drink".

Potential Claim

"In mildly dehydrated individuals, a hypotonic electrolyte drink like Hydralyte promotes faster water uptake than either (plain) water, or a high sugar sports drink".

Foot note:

Conclusion based on fluid delivery from oral consumption until 50% water absorption into the bloodstream. From a clinical study employing radio-labelled water contained in glucose-sodium solutions. (Jeukendrup AE, Currell k, Clarke J, Cole J, and Blannin K. 2009. Effect of beverage glucose and sodium content on fluid delivery. Nutrition and Metabolism 6:9-16).

The extent of water uptake is difficult to evaluate, although it appears that in dehydrated individuals, at least 2/3 of the consumed ORS is retained in the bloodstream for several hours.

Water, Glucose and Electrolyte Absorption

In discussing mechanism of uptake, we are concerned with ingredients in Hydralyte which are critical to rehydration and electrolyte replacement. These ingredients are sodium, potassium, glucose, chloride, citrate and of course water.

This knowledge is based on studies conducted on Oral Rehydration Solutions, similar drinks, and also the absorption behaviour of the individual components.

The uptake of water, glucose and electrolytes into the bloodstream is a two stage process: passage through the stomach (gastric emptying) followed by absorption at the small intestine. This brief will focus on the absorption process which tends to be rate-limiting.

The absorption of sodium and glucose is, by far, the most important mechanism because this drives water uptake; the absorption of the other active ingredients (potassium, chloride and citrate) is consequential.

Sodium is absorbed from the gastrointestinal tract into the bloodstream via the protein-based sodium-glucose co-transporter (SGLT1). There are thousands of these protein complexes per cell at the intestinal surface. The mechanism reaches a maximum rate of activity at sodium and glucose concentrations found in Hydralyte solutions **(Kellet and Helliwell, 2000).** It's fascinating to appreciate that these transporters turnover 1 molecule of glucose and 2 molecules of sodium at about 100 cycles per second **(Wright et al 2007).**

Glucose is essential to the operation of SGLT1, as it directly stimulates sodium uptake by the transporter. In fact, in the absence of glucose in a hydration beverage, sodium absorption occurs at less than 50% of the rate in the presence of the sugar **(Wright et al 2007).**

Glucose plays another intriguing regulatory role. After consuming Hydralyte, the first glucose to pass through the stomach triggers specialised sensors located on the intestinal cell surface. These sensors then up-regulate the synthesis of the SGLT1 transporters – thus accelerating the capacity for sodium, glucose and water absorption **(Dyer et al 2007).**

These facts clearly invalidate marketing statements promoting low or no sugar hydration formulations!

The optimal glucose concentration for a rehydration beverage actually sits within a narrow range. Animal studies on fluid uptake demonstrated that hypotonic solutions containing 80 – 120 mM glucose (14 – 22 g/L) produced maximal water absorption **(Farthing, 1989; Sandhu et al 1989).** Maughan, an expert in sports hydration validates this conclusion **(Maughan, RJ 1991).**

Further, too much sugar can have detrimental effects. The speed of gastric emptying falls as carbohydrate concentration increases **(Vist and Maughan, 1995)** and high sugar content can lead to feelings of stomach discomfort in athletes **(Evans et al 2009).** In this latter study, athletes rated the "feeling of being bloated" for three different glucose solutions on a 0 (comfortable) to 10 (worst) scale, 1 hour after consuming the beverage. 0% and 2% glucose were rated similarly at 2 out of 10 whereas a 10% glucose solution was reported at 6 out of 10.

There is another route of glucose absorption via GLUT2-mediated facilitated diffusion. This mechanism is linear in nature, does not appear to saturate even at concentrations over 100 mM (2%) glucose, and at such concentrations in the intestinal lumen produces an absorption rate of 2-3 times that of active transport **(Kellet and Helliwell, 2000).**

The small intestine is able to absorb around 8 Litres of water daily. The actual **mechanism of water absorption** has been debated for many years. Current hypotheses include transport of water through leaky gaps between adjacent cells, transport due to the osmotic pressure gradient or a mechanism involving the SGLT1 protein. The notion of the SGLT1 protein complex as a "water pump" has recently been rejected, although it seems that the transporter may act as a flow channel for water. **(Erokhova et al, 2016).**

Potassium absorption in the small intestine occurs by passive diffusion with a linear absorption rate over the range 3 to 8 mmol/L potassium. (120 – 300 mg/L). **(Turnburg, 1971).** Potassium absorption from Hydralyte is therefore optimal because it's concentration at 800 mg/L is well above this range. Potassium absorption is also related to water uptake through a "solvent drag" mechanism. As the rate of water absorption increases, so does potassium absorption **(Turnburg, 1971).**

Chloride and citrate absorption follows the uptake of sodium and potassium, maintaining charge balance and isotonicity across the cell membrane. **(Wright et al 2007; Fresenius Kabi, 2010).**

In conclusion, glucose in an oral rehydration solution stimulates sodium absorption. The uptake of water, potassium, chloride and citrate is simultaneous and related to sodium absorption. *[DA Note: can't really say "in proportion to" because we don't know if it is linear]*

Hydralyte contains ideal concentrations of these electrolytes and glucose.

How fast is Hydralyte taken up?

There have been no clinical studies specifically investigating uptake kinetics of Hydralyte or hypotonic ORS with similar composition (sodium at 45 – 60 mmol/L; glucose at 1.5 – 2% and osmolality in range 200 – 260 mOsm/kg). One reason for this appears to be related to research sponsorship; companies involved in marketing sports drinks, such as Gatorade and GSK, have focussed this research on high sugar beverages.

Experimental results have often been inconsistent and open to misinterpretation. For example, rapid fluid absorption in one particular section of the GI tract has been reported as if it represents water absorption in general. It's actually the overall uptake process, from swallowing the drink until fluid enters the bloodstream, which is important when comparing hydration effectiveness. Some inferences, however, can be drawn from these studies.

Perfusion Studies

One research group has been strong in the area of "perfusion studies". A permeable tube is placed into sections of the GI tract, a solution introduced, and the absorption of water and electrolytes is estimated from differences in sample concentration at the start and end of the tube. It is known that most water and electrolyte absorption occurs in the duodenum (25 cm long) and the first 50 cm length of total 250 cm, of the small intestine jejenum section.

Gisolfi et al (1992) studied the perfusion of several carbohydrate – electrolyte solutions in 8 adult men. Solutions examined included 2%, 4% and 6% glucose made isotonic (osmolality 280 mOsm/kg) with sodium chloride. (for the 2% glucose solution, sodium chloride is estimated to be about 85 mmol/L). A control, consisting of sodium chloride solution at 150 mmol/L was also employed. (Recall that Hydralyte contains only 45 to 60 mmol/L sodium chloride).

Test solutions were introduced into the duodenum via a perfusion tube at a rate of 15 ml/min over 70 minutes, equal to 1050 ml volumes in total.

Several interesting observations were made:

1. There was no difference in water absorption rate between the 2%, 4% and 6% glucose.

2. The water absorption rate for these glucose solutions (9 – 15 ml/h/cm) was at least 3 times greater than the absorption rate of the control solution, without glucose (3 ml/h/cm).

(iii) the speed of glucose uptake from the intestine increased linearly over the range 7 to 32 g/L glucose.

The key conclusion from this work is that both glucose and sodium chloride are required to maximise water absorption in the GI tract. The suggestion that this data proves that glucose-electrolyte solution is absorbed three times faster than water alone is attractive but misleading because the control was not simply water, and the experiment does not properly simulate beverage consumption under normal conditions.

The same research group studied water absorption from different sections of the small intestine in exercising athletes **(Lambert at al, 1997).** An isotonic carbohydrate – electrolyte solution was used and introduced into the stomach. The test solutions contained high sugar concentrations (2% glucose + 4% sucrose) along with 18 mmol/L sodium chloride and 3 mmol/L potassium. (Hence the solution had a greater sugar content and osmolality than Hydralyte ORS).

Surprisingly, water uptake rates were found to be very dependent on the segment of the small intestine being examined. In the 25 cm duodenum segment, fluid absorption from water alone (the control) was twice as fast as the carbohydrate-electrolyte solution (30 versus 15 ml/cm/h).

Conversely, in the 25 to 50 cm jejenum segment, fluid absorption was three times faster from the carbohydrate-electrolyte solution compared with plain water (12 ml/cm/h versus 4 ml/cm/h) although at a slower rate.

Therefore, fluid absorption in the proximal small intestine depends on the segment studied.

These results are in agreement with the known physiology of these two segments.

The duodenum, the first 25 cm of the small intestine, is considered to have leaky membranes and to be the most permeable section to water.

The early jejunum, 25 to 50 cm segment, possesses the most active glucose transport, and so water absorption is accelerated due to active glucose-sodium transport.

Where water absorption is estimated over the combined duodenum and jejunum segments, hypotonic glucose-electrolyte solutions have been shown to be moderately (~ 18%) more effective than isotonic or hypertonic solutions **(Shi et al, 1994).** Unfortunately, a water only control was not employed in this investigation.

However, it should not be forgotten that ORS such as Hydralyte present the significant advantages over water in that they promote uptake of electrolytes (sodium, potassium and chloride) and glucose. This is vital in cases of diarrheal-dehydration, and very useful during prolonged exercise, where supply of glucose into the bloodstream facilitates energy production, and electrolyte depletion can lead to unfavourable symtoms.

Radioactive labelling studies

Water uptake studies have been performed using radiolabelled water, deuterium, and measuring its accumulation in the bloodstream. The advantage of this method is that it authentically evaluates the consumption of a beverage from oral intake, through the entire GI tract, into the bloodstream. The disadvantage is that the method does not account for transfer of water from the bloodstream, into the tissues.

Jeukendrup et al (2009) investigated fluid delivery in response to sodium and glucose concentrations. Healthy male subjects fasted overnight and then rapidly consumed 600 ml volumes of different hydration beverages in the morning. Fluid uptake into the bloodstream was monitored by radioactive labelling.

All beverages contained 20 mmol/l sodium.

The beverage most similar to Hydralyte, G3, also contained 3% glucose, whereas the beverage most similar to water, G0, contained no glucose. Lastly, the beverage representative of a high sugar sports drink, G6, containing 6% glucose.

The key parameter defining water uptake rate was denoted t½, meaning the time taken for radiolabelled water to reach 50% of its maximum level in the bloodstream.

The t ½ values for G0, G3 and G6 were estimated to be 13, 10.3 and 16 minutes respectively. Consequently, the rate of water uptake for a "Hydralyte-like" solution was about 25% faster than "water" and 50% faster than the high sugar sports drink.

The maximum concentration of labelled water was detected in the bloodstream after about 30 minutes for the Hydralyte-like beverage.

This study is possibly the most relevant when it comes to describing overall water uptake rates from different solutions consumed by healthy individuals.

A second group has subsequently applied the same technique in evaluating sports beverages for water absorption and energy (carbohydrate) delivery. **(Rowlands et al 2011).**

Their findings were consistent with those of Jeukendrup et al (2009): fluid absorption was moderately faster for a hypotonic drink compared with placebo (water), isotonic (Powerade) and hypertonic (Gatorade) beverages.

These findings are in general agreement with data from a different study measuring fluid delivery from the stomach **(Vist and Maughan, 1995).** Males subjects consumed 600 ml volumes of test drink containing different levels of carbohydrates. For a drink containing 4% glucose, 50% and 80% water delivery from the stomach occurred after 17 minutes and 40 minutes respectively.

Fluid uptake will depend on the drink composition, volume, hydration status of the subjects and exercise levels undertaken.

What is the extent of fluid uptake?

No studies were found that measured actual % of fluid uptake into the bloodstream.
In fact, the extent of water uptake is difficult to evaluate because of multiple transport processes occurring (absorption, excretion, intercellular transport etc).

However, fluid retention after consumption has been evaluated in terms of hydration solutions producing the least urine output within 5 hours of consumption.

Eight athletes were dehydrated to 2% weight loss through exercise and then rapidly rehydrated with a 150% volume equivalent to the sweat losses. Volume consumed was about 2.2 Litres. Solutions containing 2% carbohydrate and variable sodium chloride (1, 30, 40 and 50 mM) were the test drinks **(Merson et al 2008).**

Urine output was monitored over a four hour period. Test drinks containing 40 and 50 mM sodium chloride presented the least urine output (800 ml = 36% intake) compared with 30 mM (1000 ml = 45% intake) and 1 mM sodium chloride (1400 m= 64% intake).

The implication is that when athletes rehydrate after exercise, the degree of fluid retention, and so hydration level, depends strongly on the sodium chloride concentration of the beverage.

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