Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2010 March ; 50(3): 269–275. doi:10.1097/MPG.0b013e3181aa3aa9.

Effects of Timing, Sex, and Age on Site-Specific Gastrointestinal Permeability Testing in Children and Adults

Mark E. McOmber, M.D.^{1,3}, Ching-Nan Ou, Ph.D.², and Robert J. Shulman, M.D.^{1,3}

¹Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital

²Department of Pathology, Baylor College of Medicine, Texas Children's Hospital

³Children's Nutrition Research Center, Houston, Texas

Summary

Objectives—Measurement of gastrointestinal (GI) permeability is used commonly in research and often clinically. Despite its utility, little is known about sugar excretion timeframes or the potential effects of age and gender in GI permeability testing. We sought to determine the timeframes of sugar excretion and the potential effects of age and gender on urinary recovery of the sugars.

Methods—Healthy adults (n=17) and children (n=15) fasted four hours after the evening meal and then ingested a solution of sucrose, lactulose, mannitol, and sucralose. Urine was collected at 30, 60, and 90 minutes after ingestion and then each time the subjects voided over the next 24 hr. Each urine void was collected separately.

Results—Median age for the adults was 47.5 yr. (range 21–57 yr.) and for children 10 yr. (5–17). There were no differences between children and adults in mean percent dose of sugar recovered. The time of peak urinary recovery of the sugars was generally similar between children and adults. Sucrose urinary recovery declined with age ($P = 0.008$; $r^2 = 0.19$) unrelated to gender. Lactulose and sucralose urinary recovery declined with age in females ($P = 0.05$, $r^2 = 0.24$ and $P = 0.011$, $r^2 = 0.41$, respectively) but not in males.

Conclusions—Overall, sugar urinary recovery is comparable in children and adults. Specific sugar urinary recovery may change as a function of age and/or gender. These results need to be taken into account when planning and interpreting GI permeability studies.

Keywords

gastrointestinal; permeability; sucrose; lactulose; mannitol; sucralose

Introduction

Gastrointestinal (GI) permeability is a measure of GI barrier function and is used frequently to assess the presence of GI mucosal injury in a number of disorders such as inflammatory bowel disease and celiac disease (1–3). It also has been used as a research tool to investigate the role of increased permeability in such disorders as inflammatory bowel disease, irritable bowel syndrome, and feeding intolerance in preterm infants (4–7). The test is safe, quantitative, and noninvasive.

The theoretical basis for the test has been reviewed extensively (1;8). In summary, the small intestinal epithelium contains a gradient of (probably three) pore sizes with the smallest being on the villus tip and the largest being in the crypt with an intermediary size along the villus base (9). These pores are passageways formed by tight junction proteins regulating movement of molecules based on size and molecular charge (8;9). Small molecules such as mannitol (a monosaccharide) are able to traverse the small pores on the villus tip but larger molecules such as the disaccharide lactulose (formed of fructose and galactose) can only move through the larger pores in the villus base and crypts (1;9). Consequently, mannitol serves as a marker of epithelial surface area whereas the ability of lactulose to permeate through the pores depends on their "leakiness" (1;8).

After absorption, the sugars enter the bloodstream. However, because the sugars are not metabolized significantly they are excreted in the urine in the same amount and ratio as they permeate the mucosa (1;10;11). If GI permeability is increased (i.e., an increase in the size of the two larger pores) the ratio of lactulose to mannitol found in the urine will be greater than that which was administered (1;10;11). By giving both sugars simultaneously and expressing the results as a ratio of lactulose to mannitol other factors such as variations in gastric emptying and intestinal transit time which might alter the amount of lactulose and mannitol appearing in the urine over a period of time were they used alone are obviated (1;10;11). Lactulose and mannitol are fermented rapidly in the colon to the same degree by the colonic microbiota and thus, measure small intestinal permeability (11).

More recently additional site-specific probes have been used. The disaccharide sucrose (formed of fructose and glucose) assesses gastric mucosal integrity because it is rapidly degraded by sucrase once it leaves the stomach (12;13). A small portion of intact sucrose is absorbed passively through the gastric mucosa (through the larger pores) and excreted unchanged in the urine (12;13).

Sucralose, a disaccharide which is used as a commercially available artificial sweetener, is synthesized by replacing three of the hydroxyl groups on sucrose with chlorine which increases its sweetness 600 times but makes it impervious to sucrase hydrolysis (11). Thus, almost all of an oral dose is excreted unchanged in the feces with a small fraction being absorbed passively through the larger pores in the small intestine and colon and excreted unchanged in the urine (14). Thus, sucralose recovery in the urine is a measure of small bowel and colonic permeability (11). If small bowel permeability is normal, it can be used to detect an increase in colonic permeability alone (11).

Both sucrose and sucralose recoveries can be expressed as a ratio of the urinary recovery of lactulose to delineate further the state of GI mucosal permeability. The sucrose/lactulose ratio increases in the presence of proximal GI injury and the sucralose/lactulose ratio increases with pure colonic injury (11-13). As in the case of the lactulose/mannitol ratio, the use of their ratios obviates issues related to gastric emptying and transit time (1;10;11). However, use of the sucrose/lactulose and sucralose/lactulose ratios presupposes that lactulose permeability is normal (i.e., the increased permeability is limited to the stomach or colon, respectively) (11-13).

Despite the usefulness of GI permeability testing and its frequency of use, there is little consensus on the timing of urine collections. For example, in measuring gastric permeability, recommended sucrose collection times have ranged from three to ten hours (6;12;15;16). To assess small intestinal permeability, collection times for lactulose and mannitol (or similar sugars) have varied from two to ten hours (16-18). In the case of colonic permeability measurements, collection times for sucralose have ranged from five to 26 hours (19-22). To our knowledge no data have been published showing the 24 hr excretion profiles of the sugars

nor the simultaneous measurement of gastric, small intestinal, and colonic permeability in humans. Finally, the potential roles that age and gender may play on permeability testing results largely remain unexplored.

The goals of our study were to determine simultaneously the 24 hr. temporal profiles of urinary recovery of sugars commonly used in GI permeability testing. Further, we sought to examine the potential role that age and gender might play in urinary recovery of the sugars.

Materials and Methods

Study Design

Subjects—Children and adults were healthy volunteers selected from family members of the faculty and staff at Baylor College of Medicine and Texas Children's Hospital in Houston, Texas. They were excluded if they had GI disease, had taken non-steroidal antiinflammatory drugs within two weeks of the study, alcohol within 48 hours of the study, or antibiotics within 4 weeks of the study, were unable to drink the sugar solution, or if they had enuresis. The study was approved by the Human Investigations Institutional Review Board and consent was obtained from the adults and assent from the children.

Permeability Testing—Subjects were instructed to drink the sugar solution following a minimum of 4 hr. of fasting after the evening meal. The sugar solution consisted of sucrose (10g), lactulose (5g), mannitol (1g), and sucralose (1g) in a volume of 127.5 mL. Following ingestion, the subjects drank an additional 240 mL of water.

Subjects voided before drinking the solution. They were instructed to try and void at 30, 60, and 90 minutes after ingestion of the solution (prior to bedtime) and then as needed. Each time the subject subsequently voided, the urine was placed in separate containers. Each container was labeled with the date and time of the void. Thymol (33 μ L of a 10% solution) was added to each container provided to the subjects as a preservative. The urine was frozen until picked up by a courier and brought to the laboratory for analysis.

After the first morning void, subjects were allowed to eat and drink (with the exception of foods containing sucralose). Urine was collected for a total of 24 hr. starting from the time of ingestion of the sugars.

Sugar Analyses—High-performance liquid chromatography was carried out to quantify the individual sugars as we and others have described (7;11;23). The assay is sensitive to 1 μ g/mL for sucrose, lactulose and mannitol and to 10 μ g/mL for sucralose. The coefficient of variation is 5%.

Calculations and Data Analysis—Data are expressed as mean $\pm$ SEM. Permeability data are expressed per body surface area (18).

Percent urinary recovery was measured for the entire 24 hr period as well as for each time point in the study. The 24 hours were split into epochs of 30 minutes for the first 90 minutes and then into blocks of 2-3 hours in order to have each individual's data points included.

The percent urinary recovery of sugar at each time point was determined by multiplying the concentration of sugar in the urine (mg/mL) by the volume of urine. The amount of excreted sugar then was divided by the mg of sugar ingested (see above). Total percent urinary recovery for the entire 24 hr period was calculated by summing the percent recoveries at each time point. Because of the difficulty in excluding sucrose from the diet, its urinary recovery was calculated only during the fasting period that lasted overnight up to and including the first morning void.

We also calculated a cumulative percent urinary recovery for each sugar. This was accomplished by normalizing the total amount of each sugar obtained over the 24 hr to 100%. The fractional amount of each sugar at each time point then was determined (i.e., fraction of 100). This allowed comparisons of urinary recovery across different subjects on the same scale (i.e., regardless of total percent recovered).

In addition to the above calculations, we also determined the ratios of the sugars as commonly used in analysis of GI permeability. The mg amount of each sugar was measured at each time point (concentration of sugar in the urine multiplied by the volume of urine) and ratios calculated by dividing by the appropriate sugar.

Differences in proportions were determined using CHI-square analysis and differences in means using Students t-test. General linear modeling techniques were used to assess the effect of gender, age, and the interaction of these on percent urinary recovery. Data not normally distributed were log transformed.

Results

Subjects

Seventeen adults and 15 children were studied. The median age for the adults was 47.5 years with a range from 21 to 57 years. The median age for the children was 10 years with a range from 5 to 17 years. The proportion of males and females in the adult and child groups did not differ (female: adults 44%, children 33%; $P = 0.55$). The number of individuals studied at each time point is shown in the Table.

Urinary Recovery of Sugars

Sucrose—The mean percent sucrose urinary recovery during the overnight fasting period was similar for children and adults ($0.14\% \pm 0.2$ vs $0.17\% \pm 0.1$, respectively). Visibly the time point of peak percent urinary recovery appeared to occur later in adults vs. children although the peak was lower for the adults than the children (Figure 1). For the majority of the adults, cumulative urinary recovery by 3 hr was greater than 50% whereas it was greater than 70% in the children (Figure 2). In contrast, by 6 hr cumulative urinary recovery in children and adults was comparable (approximately 95%, Figure 2).

Lactulose—The mean total percent lactulose urinary recovery over 24 hr. was similar for children and adults ($0.54\% \pm 0.3$ vs $0.68\% \pm 0.7$, respectively). Percent urinary recovery of lactulose began to rise and peaked earlier in adults than in children (Figure 1). However, the time point of peak percent urinary recovery for the adults was lower and broader than the children. This fit with the observation that 90% of cumulative urinary recovery was achieved by 18 hr in adults and 15 hr in children (Figure 2).

Mannitol—The mean total percent mannitol urinary recovery over 24 hr. was similar for children and adults ($35.7\% \pm 10.0$ vs $40.5\% \pm 19.0$, respectively). Percent urinary recovery of mannitol began to increase and visibly peaked earlier in adults than in children (Figure 1). However, the time point of peak percent urinary recovery was lower and broader for the adults compared to the children. Again, this fit with the observation that, similar to lactulose, 90% cumulative urinary recovery occurred by 18 hr in adults and by 15 hr in children (Figure 2).

Sucralose—The mean total percent sucralose recovered over 24 hr was similar in children and adults ($2.2\% \pm 1.3$ vs $2.9\% \pm 2.0$, respectively). Similar to the other sugars, percent urinary recovery of sucralose began to rise and visibly peaked earlier in the adults than in the children (Figure 1). Also similar to the lactulose and mannitol, the percent urinary recovery at the peak

was lower and broader for the adults compared to the children, coinciding with the observation that the cumulative percent urinary recovery was 90% or more by 21 hr in adults and by 18 hr in children (Figure 2).

Urinary Sugar Ratios

The sucrose/lactulose ratio was highest at the first measurement (30 minutes) in both children and adults and declined thereafter (Figure 3). In adults, the lactulose/mannitol ratio peaked 10-12 hr after ingestion. In contrast, in children the peak occurred at 7-9 hr after ingestion. The apparent rise at 1.5-3 hr after ingestion in children may or may not be spurious given that three children account for this time point (Figure 3). The sucralose/lactulose ratio peaked later than the lactulose/mannitol ratio; 19-21 hr after ingestion for adults and 16-18 hr for children (Figure 3).

Permeability vs. Age and Gender

There was no interaction between age and gender with regard to sucrose urinary recovery. Total percent urinary recovery over 12 hr declined with age but there was no influence of gender (Figure 4).

In contrast, there was an interaction between age and gender with regard to lactulose urinary recovery. Total percent lactulose urinary recovery over 24 hr declined with age in females but not in males (Figure 5). Similarly, the 24 hr pooled lactulose/mannitol ratio declined with age in females but not in males (Figure 5).

There was no interaction between age and gender with regard to total percent mannitol urinary recovery over 24 hr (data not shown). There also was no correlation between age or gender and total percent mannitol urinary recovery over 24 hr (data not shown).

Similar to the findings with lactulose, there was an interaction between age and gender with sucralose urinary recovery. There was a decrease in total percent sucralose urinary recovery over 24 hr with age in females but not in males (Figure 6). The sucralose/lactulose ratio showed no interaction between age and gender and no correlation with age (data not shown).

Discussion

To our knowledge, this is the first study in children and adults to delineate the temporal profiles over a 24 hr period of the urinary recovery of the sugars commonly used in permeability testing. Additionally, we evaluated the urinary recovery of the sugars simultaneously in order to compare temporal profiles among the different sugars in order to evaluate concurrently permeability in the stomach, small intestine, and colon.

By expressing the data as urinary percent dose recovered per time, we could compare directly results between children and adults. Overall, the total percent urinary recovery of the sugars over 24 hr. was similar between children and adults. However, peak urinary recovery could be seen to occur an hour or so earlier in adults, and the curves were lower in amplitude and broader than in children (Figure 1). These observations cannot be due to differences in body surface area as the data were corrected for body size. We speculate that decreased permeability with age in combination with a larger intestinal surface area which may include alterations in motility (i.e., "functional area") may account for the flatter, broader curves seen in adults compared with children.

By calculating the cumulative percent urinary recovery and normalizing this to 100%, we could not only compare results between children and adults, but also could assess better the relative urinary recovery rates among the sugars (Figure 2). As might be anticipated, sucrose urinary

recovery occurred faster than the other sugars (Figure 2). Urinary recovery was 90% or greater by 6 hr while lactulose and mannitol required 15 hr and sucralose 21 hr to reach this point (Figure 2). These findings are consistent with the physiologic differences that are the basis of using these particular disaccharides. Sucrose primarily permeates the stomach, whereas lactulose and mannitol permeate the entire small bowel, and sucralose permeates the entire small and large bowel (11).

Our data explain some of the previous observations in the literature regarding the appropriate timing of urine collections. For example, there has been debate regarding how many hours are required for an “accurate” measurement of lactulose (17;18). Based on our data, a 2 to 5 hr collection, as has been proposed in the past, might provide some comparison data for these sugars but would represent the steep slope regions for these sugars' recoveries and not include their point of maximal urinary recovery (Figure 2). Furthermore, it can be seen from our data regarding the cumulative percent urinary recovery for these sugars that earlier collections represent a very small percentage of what will ultimately be retrieved in a longer study (Figure 2). Thus, collections completed prior to this time may not be as informative.

To obviate differences due to gastric emptying or transit time, the sugars often are expressed as a ratio. Thus, we also investigated the potential effects of time on the ratios. The sucrose/lactulose ratio, representing proximal bowel permeability, quickly declined after 30 minutes because of the rapid disappearance of sucrose (Figure 3). Because a greater amount of sucrose than lactulose was given, the ratio is >1 despite the lower percent dose recovered at most time points (Figure 1).

The lactulose/mannitol ratio, representing small intestinal permeability was highest around 10-12 hr (Figure 3). The sucralose/lactulose ratio which represents colonic permeability if small bowel permeability is normal peaked later (around 19-21 hr) (Figure 3). Thus, the timing of the peak ratios appears to fit with the presumed site of absorption (11;12).

Some authors express the lactulose/mannitol ratio in terms of fractional excretion (e.g., fractional excretion of lactulose divided by fractional excretion of mannitol) (24). To convert our data to this format requires that the lactulose/mannitol ratio be divided by 5 (lactulose result/5 g ingested and mannitol result/1 g ingested; i.e., 5), the sucrose/lactulose ratio divided by 2 (sucrose result/10 g and lactulose result/5 g ingested; i.e., 2), and multiplying the sucralose/lactulose ratio by 5 (sucralose result/1 g and lactulose result/5 g ingested; i.e., 5). This conversion demonstrates similarity between our lactulose/mannitol ratio expressed as fractional excretion (0.015) and those of other investigators for normal adults (8-10 hr ratio < 0.025) (J. Meddings, personal communication, 2008).

To our knowledge, our observation that age and gender can affect permeability has not been described previously (Figures 4-6). In infants small intestinal permeability decreases with age but has been presumed to reach adult levels early in childhood (7). Sucrose, lactulose, and sucralose permeability decreased with age (Figures 4-6). In the case of sucrose children appeared to have greater permeability than did adults (Figure 4). Even if the one child with the highest sucrose permeability was excluded, the difference with age was still significant (Figure 4). In the case of sucralose, the decline with age was clearest (Figure 6).

We do not know the reason why the decline in lactulose and sucralose permeability with age was only seen in females (Figures 5 and 6). Presumably this is due to hormonal influences. It is known that the hypothalamic-pituitary-adrenocortical system including glucocorticoids and corticotropin releasing factor can alter permeability in rats as well as humans (25;26). Further studies are required to address this question directly. However, these results (Figures 4-6) stress the importance of considering age and gender in future studies of permeability.

A limitation to our study is that the individuals did not fast for the entire 24 hr period. Lactulose and mannitol can be found in small amounts in certain foods. Thus, we cannot exclude the possibility that some individuals ingested these sugars during the test. Inadvertent ingestion of lactulose or mannitol may account for some of the interindividual variation. However, we attempted to balance the need for compliance with practicality. Without a lengthy daytime fasting period we were able to include children as young as 5-years-old. Although optimal results might be achieved with a full 24 hr fast, subject acceptance of such a study undoubtedly would be low. Another potential limitation is the relatively small number of children who contributed to the 1.5-6 hr. time frame. However, this potential limitation does not alter our basic findings.

The results from our study can serve as a basis for re-examining optimal collection times to compare healthy individuals to those with abnormal permeability (e.g., inflammatory bowel disease, celiac disease, etc.). Although previous investigations have demonstrated differences in permeability between healthy individuals and those with GI and various other diseases, it is possible that by using different collection periods (e.g., time to urinary recovery plateau, overnight fasted, 24 hr) greater differences may be seen between groups with less interindividual variation. Based on Figure 2, we would suggest first testing a urinary collection time of 4 to 6 hours for sucrose and 13-15 hours for lactulose, mannitol, and sucralose in both adults and children. If a sucralose/lactulose ratio is to be measured, then based on Figure 3 the collection time might be extended to 16 to 18 hours in adults and children. Gender and age differences also must be taken into account (Figures 4-6).

Acknowledgments

The authors wish to thank Beverly Vispo and Raheela Khan for technical assistance, Erica Baimbridge for organizational assistance, and Dr. Jon Meddings for reviewing the manuscript.

This research was supported by Grant Number R01 05337 from the National Institutes of Health to RJS, the Daffy's Foundation, the USDA/ARS under Cooperative Agreement No. 6250-51000-043, and P30-DK56338 which funds the Texas Medical Center Digestive Disease Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work is a publication of the USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX. The contents of this publication do not necessarily reflect the views or policies of the USDA, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

References

1. Bjarnason I, Macpherson A, Hollander D. Intestinal permeability: an overview. *Gastroenterology* 1995;108:1566–81. [PubMed: 7729650]
2. Welcker K, Martin A, Kolle P, Siebeck M, Gross M. Increased intestinal permeability in patients with inflammatory bowel disease. *Eur J Med Res* 2004 Oct 29;9(10):456–60. [PubMed: 15546811]
3. Smecuol E, Bai JC, Vazquez H, Kogan Z, Cabanne A, Niveloni S, et al. Gastrointestinal permeability in celiac disease. *Gastroenterology* 1997 Apr;112(4):1129–36. [PubMed: 9097995]
4. Soderholm JD, Olaison G, Lindberg E, Hannestad U, Vindels A, Tysk C, et al. Different intestinal permeability patterns in relatives and spouses of patients with Crohn's disease: an inherited defect in mucosal defence? *Gut* 1999 Jan;44(1):96–100. [PubMed: 9862833]
5. Dunlop SP, Hebden J, Campbell E, Naesdal J, Olbe L, Perkins AC, et al. Abnormal intestinal permeability in subgroups of diarrhea-predominant irritable bowel syndromes. *Am J Gastroenterol* 2006 Jun;101(6):1288–94. [PubMed: 16771951]
6. Shulman RJ, Eakin MN, Czyzewski DI, Jarrett M, Ou CN. Increased gastrointestinal permeability and gut inflammation in children with functional abdominal pain and irritable bowel syndrome. *J Pediatr* 2008 Nov;153(5):646–50. [PubMed: 18538790]

7. Shulman RJ, Schanler RJ, Lau C, Heitkemper M, Ou C-N, Smith EO. Early feeding, antenatal glucocorticoids, and human milk decrease intestinal permeability in preterm infants. *Pediatr Res* 1998;44:519–23. [PubMed: 9773840]
8. Teshima CW, Meddings JB. The measurement and clinical significance of intestinal permeability. *Curr Gastroenterol Rep* 2008 Oct;10(5):443–9. [PubMed: 18799118]
9. Fihn BM, Sjoqvist A, Jodal M. Permeability of the rat small intestinal epithelium along the villus-crypt axis: effects of glucose transport. *Gastroenterology* 2000 Oct;119(4):1029–36. [PubMed: 11040189]
10. Travis S, Menzies I. Intestinal permeability: functional assessment and significance. *Clin Sci* 1992;82:471–88. [PubMed: 1317756]
11. Meddings JB, Gibbons I. Discrimination of site-specific alterations in gastrointestinal permeability in the rat. *Gastroenterology* 1998;114:83–92. [PubMed: 9428222]
12. Meddings JB, Sutherland LR, Byles NI, Wallace JL. Sucrose: a novel permeability marker for gastroduodenal disease. *Gastroenterology* 1993;104:1619–26. [PubMed: 8500718]
13. Vera JF, Gotteland M, Chavez E, Vial MT, Kakarieka E, Brunser O. Sucrose permeability in children with gastric damage and *Helicobacter pylori* infection. *J Pediatr Gastroenterol Nutr* 1997;24:506–11. [PubMed: 9161942]
14. Roberts A, Renwick AG, Sims J, Snodin DJ. Sucralose metabolism and pharmacokinetics in man. *Food Chem Toxicol* 2000;38:S31–S41. [PubMed: 10882816]
15. Ekenel M, Avsar E, Imeryuz N, Yuksel M, Haklar G, Kocakaya O, et al. Effects of selective COX-2 inhibitors on the gastric permeability of sucrose: a controlled study with placebo and ibuprofen. *Eur J Gastroenterol Hepatol* 2003 Apr;15(4):403–6. [PubMed: 12655261]
16. Lowe CE, Depew WT, Vanner SJ, Paterson WG, Meddings JB. Upper gastrointestinal toxicity of alendronate. *Am J Gastroenterol* 2000 Mar;95(3):634–40. [PubMed: 10710050]
17. Akram S, Mourani S, Ou CN, Rognerud C, Sadiq R, Goodgame RW. Assessment of intestinal permeability with a two-hour urine collection. *Dig Dis Sci* 1998 Sep;43(9):1946–50. [PubMed: 9753256]
18. Nathavitharana KA, Lloyd DR, Raafat F, Brown GA, McNeish AS. Urinary mannitol:lactulose excretion ratios and jejunal mucosal structure. *Arch Dis Child* 1988;63:1054–9. [PubMed: 3140738]
19. Anderson AD, Jain PK, Fleming S, Poon P, Mitchell CJ, MacFie J. Evaluation of a triple sugar test of colonic permeability in humans. *Acta Physiol Scand* 2004 Oct;182(2):171–7. [PubMed: 15450113]
20. Farhadi A, Gundlapalli S, Shaikh M, Frantzides C, Harrell L, Kwasny MM, et al. Susceptibility to gut leakiness: a possible mechanism for endotoxaemia in non-alcoholic steatohepatitis. *Liver Int*. 2008 Apr 5;
21. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von HS, et al. Altered intestinal function in patients with chronic heart failure. *J Am Coll Cardiol* 2007 Oct 16;50(16):1561–9. [PubMed: 17936155]
22. Suenaeert P, Bulteel V, Den HE, Geypens B, Monsuur F, Luypaerts A, et al. In vivo influence of nicotine on human basal and NSAID-induced gut barrier function. *Scand J Gastroenterol* 2003 Apr;38(4):399–408. [PubMed: 12739712]
23. Catassi C, Pierani P, Natalini G, Gabrielli O, Coppa GV, Giorgi PL. Clinical application of a simple HPLC method for the sugar intestinal permeability test. *J Pediatr Gastroenterol Nutr* 1991 Feb;12(2):209–12. [PubMed: 1904934]
24. Fries W, Renda MC, Lo Presti MA, Raso A, Orlando A, Oliva L, et al. Intestinal permeability and genetic determinants in patients, first-degree relatives, and controls in a high-incidence area of Crohn's disease in Southern Italy. *Am J Gastroenterol* 2005 Dec;100(12):2730–6. [PubMed: 16393227]
25. Wallon C, Yang PC, Keita AV, Ericson AC, McKay DM, Sherman PM, et al. Corticotropin-releasing hormone (CRH) regulates macromolecular permeability via mast cells in normal human colonic biopsies in vitro. *Gut* 2008 Jan;57(1):50–8. [PubMed: 17525093]
26. Filaretova L. The hypothalamic-pituitary-adrenocortical system: Hormonal brain-gut interaction and gastroprotection. *Auton Neurosci* 2006 Apr 30;125(12):86–93. [PubMed: 16481222]

Figure 1.

Percent urinary recovery of sucrose (top left), lactulose (top right), mannitol (bottom left), and sucralose (bottom right) at each time point (mean $\pm$ SEM)

Figure 2.
Cumulative urinary recovery of sucrose, lactulose, mannitol, and sucralose normalized to 100%
(mean $\pm$ SEM)

Figure 3. Sugar ratios at each time point (mean $\pm$ sem). Sucrose/lactulose (top left), lactulose/mannitol (top right), and sucralose/lactulose (bottom left)

Figure 4.

Sucrose permeability vs. age. Sucrose permeability (percent urinary recovery) declined as a function of age. The data are log transformed.

Figure 5.

Lactulose permeability and lactulose/mannitol ratio vs. age. Lactulose permeability (percent urinary recovery) and the lactulose/mannitol ratio declined with age in females but not in males.

Figure 6. Sucralose permeability vs. age. Sucralose permeability (percent urinary recovery) declined with age in females but not in males.

Table

Number of Subjects at Each Time Point

Time (hr)	Adults	Children
0-0.5	16	14
0.5-1	15	15
1-1.5	14	15
1.5-3	3	3
4-6	8	2
7-9	17	5
10-12	13	12
13-15	14	10
16-18	12	9
19-21	9	9
22-24	7	7