

The sensitivity of the lactulose/rhamnose gut permeability test

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Abstract

Background The lactulose/rhamnose (L/R) intestinal permeability test is widely used. However, different quantities and proportions of lactulose and rhamnose are used. The aim of this study was to determine whether a low dosage of lactulose is able to discriminate between normal and increased permeability.

Materials and methods Two groups of 10 healthy subjects were studied. In group 1, three different iso-osmolar test solutions were administered on 3 days. The solutions consisted of 10 g of L with 1 g of R, 5 g of L with 0.5 g of R and 1 g of L with 0.1 g of R in 65 mL of water. Group 2 ingested these solutions 1 h after ingestion of 750 mg of chenodeoxycholic acid (CDCA), which is known to increase permeability. The urinary L/R ratio was determined using high-performance liquid chromatography. Data are presented as medians (range).

Results In group 1, no differences were observed between the three solutions. In Group 2, there was a significant difference ($P = 0.045$) between the three solutions. The L/R ratios were 0.0079 (0.0024–0.0152) (1L to 0.1R), 0.0138 (0.0066–0.0192) (5L to 0.5R) and 0.0144 (0.0074–0.0374) (10L to 1R). The L/R ratio differed significantly between Groups 1 and 2 ($P < 0.001$) using the 5L to 0.5R and 10L to 1R solutions respectively.

Conclusion If the permeability is increased, the urinary L/R ratio depends on the quantity of lactulose and rhamnose administered in equal proportion. 5L to 0.5R is sufficient to discriminate between a normal and a moderately increased permeability.

Keywords Chenodiol, intestinal permeability, lactulose/rhamnose ratio, sensitivity.
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Introduction

The intestinal permeability can be evaluated by measuring the urinary excretion of orally administered water-soluble, non-degradable test molecules. This barrier function test is based on the comparison of intestinal permeation of a larger molecule with that of a smaller molecule by measuring the ratio of urinary excretion of these molecules. These two molecules follow different routes of intestinal

permeation: the larger molecules are assumed to permeate paracellularly, and the smaller molecules are assumed to permeate transcellularly. Preabsorption factors such as gastric emptying, dilution by secretion and intestinal transit time, and post-absorption factors such as systemic distribution and renal clearance are assumed to affect both molecules equally. Therefore, the urinary excretion ratio is considered to be a parameter for intestinal permeability *per se* [1–3].

Knowledge about the intestinal barrier function has implications for the aetiology and the pathogenesis of various intestinal and systemic disorders, such as coeliac disease [4–6], inflammatory bowel disease [7–10], immunodeficiency syndromes [11–13], ankylosing spondylitis [14], cystic fibrosis [15,16], iron deficiency [17], atopic eczema [18,19], cardiopulmonary bypass [20–22], kwashiorkor [23,24], ileostomy [25], viral hepatitis [26], viral gastroenteritis [27], diabetes mellitus [28] and food allergy [29].

Some drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) [30–32], cytostatics [33,34] and cholagogues [35], have been reported to increase intestinal permeability.

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Other factors that can increase intestinal permeability are alcohol abuse [36], enteral feeding [37,38], prolonged parenteral nutrition [39] and strenuous exercise [40–43].

Several molecules for the determination of intestinal permeability have been described. The larger molecules are usually disaccharides, such as lactulose or cellobiose. Other molecules such as [^{51}Cr]-EDTA, [$^{99\text{m}}\text{Tc}$]-DPTA, polyethylene glycols (PEGs) and dextran have also been used. The smaller molecules are usually the monosaccharides rhamnose or mannitol [1–3].

A comprehensive search through Medline until 1997 revealed more than 1200 publications in which intestinal permeability was studied. In more than 280 human studies mannitol was used as the smaller molecule. However, if the search was restricted to studies in which human intestinal permeability was determined using lactulose and rhamnose as the test molecules, more than 60 publications were retrieved. After a detailed examination of these publications it was found that lactulose and rhamnose were used in various dosages. The most common combination of lactulose and rhamnose was 5 g of lactulose with 1 g of rhamnose (see Refs 4,7,8,12–15,20–23,25,26,33,37,38,44–55). Other regimens were 5 g of lactulose with 0.75 g of rhamnose [18,56], 5 g of lactulose with 0.5 g of rhamnose [11], 2.3 g of lactulose with 0.5 g of rhamnose [5,6], 3.5 g of lactulose with 0.5 g of rhamnose [17,27,57], 7.5 g of lactulose with 1 g of rhamnose [9], 5 g of lactulose with 5 g of rhamnose [58], 11.25 g of lactulose with 1 g of rhamnose [10], 0.1 g of lactulose kg^{-1} bodyweight with 0.02 g of rhamnose kg^{-1} bodyweight [19], 6.7 g of lactulose with 1 g of rhamnose [59], 13.7 mmol lactulose with 6.1 mmol rhamnose [60], 10 g of lactulose with 5 g of rhamnose [35], 10 g of lactulose with 1 g of rhamnose [61], 7 g of lactulose with 1 g of rhamnose [27] and 5.3 g of lactulose with 0.75 g of rhamnose [16]. The reason for these differences may be the local availability of analysis techniques.

The question arises whether the quantity of lactulose and rhamnose affects the sensitivity of the lactulose/rhamnose permeability test for determination of a condition in which the intestinal permeability is increased; in other words, it is unknown whether the administered dosage of lactulose/rhamnose influences the outcome of this test under conditions of increased intestinal permeability. Therefore, the aim of the present study was to investigate which dosage of lactulose and rhamnose is optimal for determination of increased permeability. Therefore, we compared the urinary lactulose/rhamnose ratio after administration of three different dosages of lactulose/rhamnose in a constant proportion with each other under normal conditions, and under conditions of increased permeability, which were artificially induced by administration of 750 mg of a choleretic compound, chenodeoxycholic acid (chenodiol) [35].

Subjects and methods

Two groups of 10 healthy, non-smoking subjects (five men

and five women) were studied (age 25 years, range 11). The study was approved by the medical ethics committee of the University Hospital. All subjects gave their written informed consent to participate in the study.

Group 1 (control)

Three different test solutions were randomly administered on three different testing days. All tests were separated by a washout period of at least 72 h and were performed in the morning after an overnight fast. The test solutions consisted of 1 g of lactulose (Centrafarm syrup, 670 mg mL^{-1} , Etten-Leur) with 0.1 g of L-rhamnose (Sigma Chemical, USA) (solution A), 5 g of lactulose with 0.5 g of rhamnose (solution B) and 10 g of lactulose with 1 g of rhamnose (solution C) dissolved in 65 mL of water. The test solutions were made iso-osmolar using sucrose (Sigma Chemical).

Group 2 (chenodiol)

To evaluate the effect of chenodiol on the lactulose/rhamnose ratio, solution B was administered as a control solution. Subsequently, the subjects randomly ingested the same test solutions as Group 1 on three different testing days 1 h after ingestion of a single dosage of 750 mg of chenodiol (three 250-mg tablets, Chenofalk, Germany), which is known to increase intestinal permeability [35]. The subjects were not allowed to consume alcoholic beverages, to use drugs, except oral contraceptives, or to perform intensive physical exercise the day before testing. Before each solution was ingested, the subjects emptied their bladder. Urine was collected for 5 h, and during this period the subjects were not allowed to eat or drink. The volume was recorded, and urine samples were stored at -80°C . The urinary lactulose and rhamnose excretion was determined by a validated, sensitive, newly developed fluorescent detection high-performance liquid chromatography (HPLC) system [62], and the lactulose/rhamnose ratio was calculated.

Statistics

Data are presented as medians (range). Comparisons between the test solutions were carried out using Friedman and Wilcoxon non-parametric tests. Differences between Groups 1 and 2 were assessed using the Mann–Whitney and Kruskal–Wallis non-parametric tests. All statistical analyses were performed using the SPSS 7.5 for Windows package.

Results

Figure 1 shows the effect of 750 mg of chenodiol on the lactulose/rhamnose ratio in the individuals from Group 2

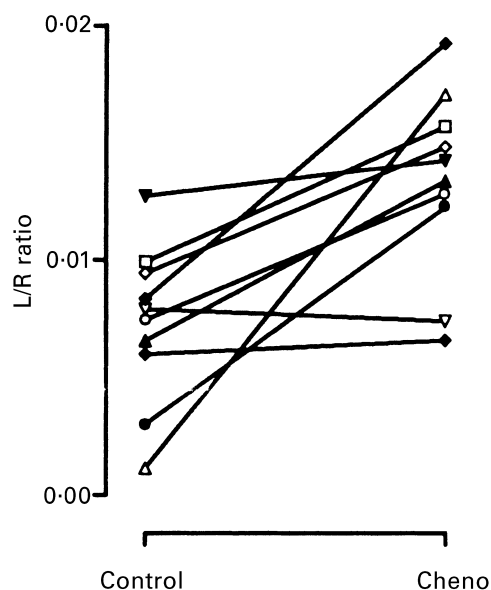


Figure 1 The effect of a single dose of 750 mg of chenodiol on the lactulose/rhamnose ratio in the individuals from group 2 ($n=10$).

using 5 g of lactulose with 0.5 g of rhamnose. Seven subjects had a strong response on chenodiol administration, two subjects had a small response, and one subject had no response. The lactulose/rhamnose ratio increased from 0.0081 (0.0012–0.013) to 0.0138 (0.0066–0.0190), ($P=0.007$).

Differences in the lactulose/rhamnose ratio were determined between the three test solutions (Fig. 2). In group 1 (control) no significant differences could be observed between the three test solutions [solution A, 0.0031 (0.0009–0.0198); solution B, 0.0035 (0.0016–0.0080); solution C, 0.0018 (0.0012–0.0039), $P=0.26$]. In group 2

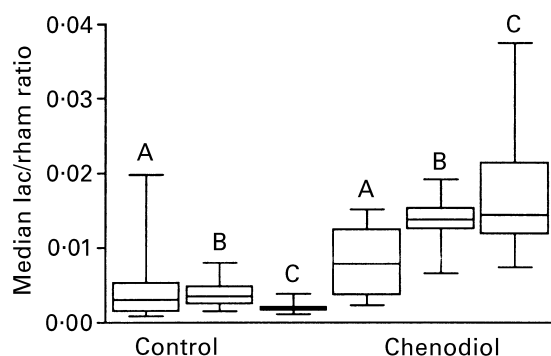


Figure 2 The median lactulose/rhamnose ratios of Group 1 (control, $n=10$) and Group 2 (chenodiol, $n=10$) for the three different solutions. Group 1 shows no significant differences between the three test solutions. Group 2 showed a significant difference between solution A and B ($P=0.013$) and between solution A and C ($P=0.022$). There was a significant difference in the lactulose/rhamnose ratio between Group 1 and Group 2 for solution B ($P<0.001$) and solution C ($P<0.001$).

2 (chenodiol), after ingestion of chenodeoxycholic acid there was a significant difference ($P=0.045$) in the lactulose/rhamnose ratio between the three test solutions [solution A, 0.0079 (0.0024–0.0152); solution B, 0.0138 (0.0066–0.0192); solution C, 0.0144 (0.0074–0.0374)]. Wilcoxon's analysis showed a significant difference between solution A and solution B ($P=0.013$), and between solution A and solution C ($P=0.022$). The lactulose/rhamnose ratio in Group 1 and Group 2 after chenodiol administration differed significantly using solution B ($P<0.001$) and solution C ($P<0.001$), but not when solution A was used ($P=0.096$).

The urinary recoveries of lactulose and rhamnose in both groups are displayed in Table 1. There was a significant difference in rhamnose recovery between the three different solutions in Groups 1 ($P=0.025$) and 2 ($P<0.001$). In group 1, Wilcoxon's analysis showed a difference in rhamnose recovery between solution A and solution B ($P=0.017$), and between solution A and solution C ($P=0.009$). In Group 2, there was also a difference between solution A and solution B ($P=0.005$), and between solution A and solution C ($P=0.008$).

Kruskal–Wallis comparisons between the groups showed a significant difference in lactulose recovery between solution B ($P=0.002$) and solution C ($P<0.001$).

Discussion

Measurement of small bowel permeability by quantifying the urinary excretion of water-soluble, non-degradable test molecules is widely used as a non-invasive method to determine alterations in the intestinal mucosal integrity in various diseases. A literature search showed that lactulose and rhamnose have been used. However, various quantities of these molecules are used. Other molecules, such as mannitol, have also been used in various quantities for the determination of changes in intestinal permeability. As it is unknown whether the test molecules, administered in a certain dosage, have identical sensitivity in determining changes in intestinal permeability, we performed a study in which we restricted ourselves to a comparison of three different dosages of lactulose and rhamnose, administered in equal proportion, under normal conditions and under conditions of increased permeability.

We artificially increased the lactulose/rhamnose ratio using oral chenodeoxycholic acid administration. This is an unconjugated bile acid used for the medical dissolution of gallstones. In the majority of healthy subjects, a single dosage of chenodiol acutely injures the small intestinal mucosa, leading to increased permeability.

Under conditions of a normal permeability, no difference in the lactulose/rhamnose ratio could be observed after administration of 10 g of lactulose with 1 g of rhamnose, compared with 5 g of lactulose with 0.5 g of rhamnose, and with 1 g of lactulose with 0.1 g of rhamnose. The proportion to which lactulose and rhamnose is absorbed, as reflected by the recovery data, is equal after administration

Table 1 Urinary recoveries (median (range)) of lactulose and rhamnose in both groups after ingestion of three different solutions

	Solution A	Solution B	Solution C
Group 1			
Per cent lactulose recovery	0.11 (0.55–0.83)	0.075 (0.04–0.14)	0.049 (0.028–0.83)
Per cent rhamnose recovery	12.4 (6.8–24.1)	7.3 (2.1–9.4)	7.0 (4.2–10.1)
Group 2			
Per cent lactulose recovery	0.17 (0.11–0.81)	0.30 (0.03–0.39)	0.28 (0.09–0.80)
Per cent rhamnose recovery	11.9 (2.6–17.9)	5.7 (1.4–8.6)	5.6 (2.0–9.7)

Rhamnose recoveries in Group 1 and Group 2 differed significantly ($P = 0.025$ and $P < 0.001$ respectively; $n = 10$). Group 1 showed a significant difference in rhamnose recovery between solutions A and B ($P = 0.017$), and between solutions A and C ($P = 0.009$). Group 2 showed a significant difference in rhamnose recovery between solution A and B ($P = 0.005$) and between solutions A and C ($P = 0.008$). Between the groups there was a significant difference in lactulose recovery between solution B ($P = 0.002$) and solution C ($P < 0.001$).

of all three test solutions, suggesting a linear dosage–absorption kinetics for both molecules. Under conditions of increased permeability, however, the ability of the intestinal mucosa to absorb rhamnose is decreased relative to lactulose absorption, reflected by an increased lactulose/rhamnose ratio. If the quantity of lactulose and rhamnose that is presented to the intestinal mucosa is increased, the ability of the intestinal mucosa to absorb lactulose appears to be relatively higher than the ability to absorb rhamnose. This is reflected by the recovery data, which show an unchanged lactulose recovery at higher dosages of lactulose and rhamnose. The rhamnose recovery, however, decreases if the dosages of lactulose and rhamnose are higher, thus leading to an increasing lactulose/rhamnose ratio. This suggests that, if intestinal permeability is increased, lactulose and rhamnose show different absorption kinetics.

Rhamnose absorption is assumed to be a passive, paracellular process with linear dosage–absorption kinetics. Lactulose, however, is assumed to pass the intestinal mucosa via the paracellular route between the intestinal cells via the tight junctions [1,3]. The present study shows that the dosage–absorption kinetics is a non-linear function; if the permeability is increased, the lactulose/rhamnose ratio is higher if higher dosages of the molecules in equal proportion are applied. Although it is assumed that pre- and post-absorptive factors do not influence the outcome of the lactulose/rhamnose permeability test, the recovery data demonstrate that, under conditions of increased permeability, a higher dosage of lactulose and rhamnose leads to unchanged lactulose recovery and decreased rhamnose recovery. This suggests the possible involvement of pre- or post-absorptive factors other than paracellular diffusion if the permeability is increased. Lactulose, for instance, accelerates intestinal transit [63], thus leading to a decreased time of exposure of both molecules to the intestinal mucosal surface.

The present study clearly demonstrates that, in a situation in which the permeability is increased in a controlled setting, the quantity of administered lactulose and rhamnose is an important factor in the assessment of a change in the lactulose/rhamnose ratio. This finding is of clinical

significance because it demonstrates that standardization of this test is required for proper interpretation and for comparisons between studies. As other molecules such as mannitol, PEG, [^{51}Cr]-EDTA, [$^{99\text{m}}\text{Tc}$]-DPTA, dextran and cellobiose share the same paracellular and transcellular permeation routes as lactulose and rhamnose, it may be reasonable to assume that the absolute quantities of these other molecules and their proportions are also an important factor in the assessment of a change in permeability.

Because of the prokinetic effect of lactulose [63], it is recommended that the quantity of lactulose administered is reduced as much as possible in the measurement of intestinal permeability in order to prevent gastrointestinal symptoms. In our study a dosage of 5 g of lactulose with 0.5 g of rhamnose was sufficient to discriminate significantly between a moderate increased permeability induced by chenodiol and a normal permeability.

Studies to validate our results in patients with increased permeability should be carried out in the future.

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