

# Influence of oro-caecal transit time on hydrogen excretion after carbohydrate malabsorption

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**SUMMARY** The aim of the present study was to determine whether changes in oro-caecal transit time (OCTT) affect the magnitude of the breath hydrogen (H<sub>2</sub>) excretion after ingestion of unabsorbable carbohydrate. We studied eight healthy subjects by interval sampling of end expiratory H<sub>2</sub> concentration for 12 hours after ingestion of: (1) 10 g lactulose (L); (2) 10 g L with 20 mg metoclopramide (M) as tablets; (3) 20 g L, and (4) 20 g L with 7.5 mg diphenoxylate (D) as tablets, in random order. In spite of significant changes in OCTT after M and D, there were no significant changes, compared for the same dose of lactulose, with respect to area under the breath H<sub>2</sub> excretion curves, peak increments of H<sub>2</sub> concentration or timing of the peak increment. We conclude that, within the ranges observed, the OCTT does not significantly affect the shape of the H<sub>2</sub> concentration *versus* time curves. In comparative studies estimates of the degree of carbohydrate malabsorption on the basis of breath H<sub>2</sub> concentration may be valid in spite of differences in OCTT.

Breath hydrogen (H<sub>2</sub>) tests in the form of interval sampling of end expiratory H<sub>2</sub> concentrations are widely used in studies of carbohydrate absorption. Quantitative estimates of the amount of carbohydrate malabsorbed from a given test meal is generally obtained by comparing the areas under the breath H<sub>2</sub> excretion curves after different meals or by comparing with the area obtained after a given dose of the non-absorbable disaccharide lactulose.<sup>1-6</sup> This procedure implies that extrapolation of data from the more simple interval sampling of H<sub>2</sub> concentrations<sup>7</sup> to quantitative measurements of total H<sub>2</sub> excretion<sup>8</sup> is valid. It has been suggested that quantitative estimates of carbohydrate malabsorption are valid on the basis of breath H<sub>2</sub> concentration only if it is assumed that the colonic entry rate of the test carbohydrate and lactulose is equivalent.<sup>9</sup> This suggestion could challenge the validity of quantitative estimates of carbohydrate malabsorption when significant differences of the oro-caecal transit times between different test meals exist. The relationship between upper intestinal transit *per se*, however, and colonic H<sub>2</sub> production is not known. We have therefore investi-

gated the effect of pharmacologically induced changes in oro-caecal transit time on the H<sub>2</sub> excretion as measured by interval sampling of end expiratory breath H<sub>2</sub> concentrations after different loads of lactulose.

## Methods

### SUBJECTS

Eight healthy adults (seven men and one woman, aged 21-33 years) were studied. The subjects were taking no other medication including antibiotics, salicylates and laxatives, they had no history of recurrent or present chronic gastrointestinal or pulmonary disease. No subjects had lactose intolerance. All subjects were H<sub>2</sub> producers ( $\geq 10$  ppm sustained rise of H<sub>2</sub> concentration after 10 g lactulose with 100 ml tap water). Blood screening tests were normal.

### BREATH TESTS

Breath H<sub>2</sub> excretion was measured by interval sampling of end expiratory H<sub>2</sub> concentrations on a GMI (Gas Measurements Instruments Ltd, Renfrew, Scotland) H<sub>2</sub> monitor.<sup>10</sup> After at least 12 hours overnight fast, the subjects had a mouth rinse with a 0.1% chlorhexidine solution for two minutes,

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thereafter repeated, and ended with a tap water swill.<sup>11,12</sup> In all breath tests end expiratory H<sub>2</sub> concentrations were collected in duplicate from the mouth in 20 ml plastic syringes (Once<sup>R</sup>) fitted with a Y-piece. Samples were taken before lactulose ingestion and every 15 minutes for seven hours and immediately analysed. The study was extended to 12 hours, and during the last five hours samples were taken every 30 minutes in Becton-Dickinson<sup>R</sup> 20 ml plastic syringes, which were stored overnight at 5°C for analysis the next morning.<sup>13</sup> Smoking and sleeping was not allowed and the subjects were non-ambulant. During the study period and for the 24 hours after each test the subjects completed a standardised symptom score.<sup>4</sup>

#### DESIGN OF THE STUDY

All breath tests were carried out within a period of two months and were coordinated with a separate study of quantifying carbohydrate malabsorption (Rumessen *et al*, in preparation). A minimum of six days elapsed between the difference tests to avoid colonic bacterial metabolic changes.<sup>14,15</sup> All subjects initially received 10 g (15 ml) lactulose (SAD) in 100 ml water. The lactulose solution contained 667 mg lactulose, 60 mg lactose, and 110 mg galactose per ml (according to the supplier). Subsequently the following tests were performed in random order: (1) 10 g lactulose in 100 ml water; (2) 10 g lactulose in 100 ml water and 20 mg metoclopramide (Primperan<sup>R</sup>) as tablets 45 minutes before the test solution. Each tablet of 10 mg contained 34 mg lactose (according to the supplier); (3) 20 g lactulose in 200 ml water;

Table Hydrogen excretion after changes of oro-caecal transit time (OCTT) of different lactulose (L) loads with 20 mg metoclopramide (M) or 7.5 mg diphenoxylate (D) in eight subjects

	OCTT (min)	AUC§ (ppm × min × 10 <sup>-2</sup> )	Peak-H <sub>2</sub> § (ppm)	t-peak§ (min)
10 g L	90* (68–150)‡	125 (91–164)	60 (41–68)	75 (45–90)
10 g L+M	45* (30–56)	106 (56–178)	44 (30–66)	128 (38–214)
20 g L	60†‡ (15–75)	243 (182–334)	78 (56–126)	150 (90–206)
20 g L+D	75† (45–105)	187 (137–345)	73 (60–93)	143 (75–214)

\*The OCTT was significantly shorter after M ( $p < 0.01$ ); †The OCTT was significantly longer after D ( $p < 0.05$ ); ‡The OCTT of 10 g L was significantly longer compared with 20 g L ( $p < 0.05$ ); §For the same lactulose loads there were no significant differences ( $p > 0.10$ ) AUC: Area under the H<sub>2</sub> excretion curve from OCTT to 12 hours minus area under lowest previous value in the same period. Peak-H<sub>2</sub>: Maximal rise of H<sub>2</sub> concentration during study period. t-peak: Time from OCTT to peak-H<sub>2</sub>. Results are given as medians (interquartile ranges).

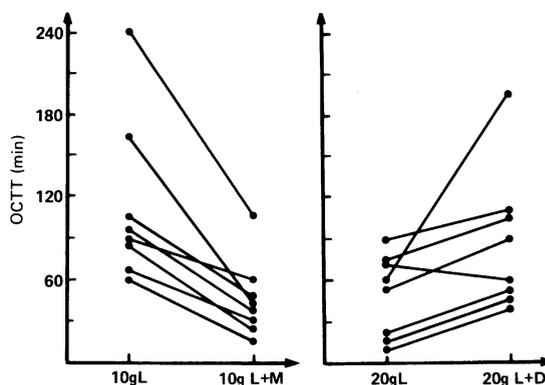


Figure Effect of 20 mg metoclopramide (M) and 7.5 mg diphenoxylate (D) as tablets on the oro-caecal transit times (OCTT) of different doses of lactulose (L) ( $p < 0.01$  (M),  $p < 0.05$  (D)).

(4) 20 g lactulose in 200 ml water and 7.5 g diphenoxylate (Retardin<sup>R</sup>) as tablets, 45 minutes before the test solution. Each tablet of 2.5 mg contained 25 microgram atropine and 145 mg lactose (according to the supplier); (5) Fasting except for tap water without restrictions. During the course of all tests (incl no 5) a standardised meal consisting of 100 g minced meat stew together with 50 g boiled rice and 150 ml tap water was given within four hours, but never before the oro-caecal transit time was determined. The meal was consumed within a period of 15 minutes.

This meal caused no significant H<sub>2</sub> production neither at ingestion nor during the rest of the study period (Rumessen *et al*, in preparation).

#### CALCULATIONS AND STATISTICS

The following variables were determined and compared for the same dose of lactulose: (1) Oro-caecal transit time (OCTT), as the interval between ingestion and the initial sustained rise in breath H<sub>2</sub> concentration of 10 ppm or more;<sup>16</sup> (2) Maximal rise of H<sub>2</sub> concentration from lowest previous values (peak-H<sub>2</sub>); (3) Time in minutes from OCTT to peak H<sub>2</sub> (t-peak); (4) Area under the H<sub>2</sub> concentration *versus* time curves from the OCTT according to the trapezoidal rule (AUC). AUC's were calculated as: (a) Area under the curve minus area under the lowest previous values; (b) Area under the curve minus area under each individual fasting curve.

These areas were calculated for the first two and four hours of the sustained increase in H<sub>2</sub> concentration as well as for the whole period from OCTT to 12 hours. Baseline H<sub>2</sub> concentrations were not reached in two subjects after 20 g lactulose and in two others after 20 g lactulose + diphenoxylate. The small additional areas were calculated by extrapolation to base line.

We furthermore compared the OCTT of 10 g lactulose with that of 20 g lactulose. The reproducibility of the initial 10 g lactulose load and the 10 g load used for calculation and comparison is reported elsewhere (Rumessen *et al*, in preparation).

#### STATISTICAL ANALYSIS

We used non-parametric statistics (Pratt's test, Spearman's rank correlation analysis), and the results were consequently expressed as medians and inter-quartile ranges.  $p < 0.05$  was considered significant.

#### ETHICS

The study was carried out in accordance with the Helsinki Declaration II, and the study protocol was approved by the Copenhagen County medical ethics committee.

#### Results

Our results are summarised in the Table.

A significant shortening of OCTT was observed after metoclopramide ( $p < 0.01$ ) and OCTT's were significantly increased after diphenoxylate ( $0.01 < p < 0.05$ ) (Figure, Table). The difference in OCTT between 10 g lactulose and 20 g lactulose was significant ( $0.01 < p < 0.05$ ) (Table). Irrespective of method of calculation, for the same dose of lactulose the changes in AUC's or peak- $H_2$  when metoclopramide or diphenoxylate was given were not significant ( $p > 0.10$ ). There was, however, a tendency towards lower  $H_2$  excretion after diphenoxylate (Table). Similarly, there were no significant changes in timing of the peak- $H_2$  value when metoclopramide or diphenoxylate was given ( $p > 0.10$ ) (Table). Irrespective of whether metoclopramide or diphenoxylate was taken, there was no overall correlation between OCTT and  $H_2$  production for each dose of lactulose ( $p > 0.50$ ). The AUC's and  $H_2$ -peaks of the initial 10 g lactulose load and the 10 g lactulose load used for randomised comparison were not significantly different ( $p > 0.10$ ), and indicated no change of the overall  $H_2$ -excretion pattern during the study. Apart from one subject complaining of moderate borborygmia after 20 g lactulose, the gastro-intestinal symptoms were scored as none or mild in all studies with no differences between the test meals. No adverse drug reactions were noted.

#### Discussion

The present findings indicate that significant changes of the OCTT do not significantly influence the  $H_2$  excretion as measured by interval sampling of end expiratory  $H_2$  concentrations after different lactulose loads. There were no indications of changes in the

overall  $H_2$  excretion pattern during the study period, and the results are not likely to be explained by colonic adaptation or other period effects. There is no evidence suggesting an effect of metoclopramide or diphenoxylate/atropine on colonic bacterial metabolism and metoclopramide seems to have little effect on motility of the large intestine.<sup>17</sup> The lactose content of the tablets was negligible and irrelevant. Although the material is small and the data show rather large variation, it seems justified to conclude that the OCTT *per se*, within the ranges observed, does not significantly influence the overall pattern of  $H_2$  excretion. Quantitative estimates of carbohydrate malabsorption, whether expressed as AUC's or peak increments of  $H_2$  production, may therefore be widely independent of the OCTT's of the substances compared. There was, however, a tendency towards lower  $H_2$  excretion after diphenoxylate, but no tendencies were apparent after metoclopramide, although this substance had the greatest effect on OCTT. We cannot, however, exclude the possibility that more extreme differences in transit times may unmask an influence on  $H_2$  excretion in a larger sample size, and it is not possible to control all conceivable confounding factors in a study like this.

It is essential for the validity of breath  $H_2$  tests that the  $H_2$  response to a given load of malabsorbed carbohydrate is rather insensitive to changes of the OCTT within physiological ranges. This is so because: (1) One of the main determinants of OCTT is indeed the malabsorbed amount of carbohydrate itself.<sup>18</sup> This is illustrated in the present study by the significantly shorter transit times of 20 g lactulose loads compared with 10 g doses. This confirms earlier findings,<sup>16,18</sup> and was indeed the reason why we used different doses of lactulose for metoclopramide and diphenoxylate to exert their effects upon. If, therefore, breath  $H_2$  tests were very sensitive to changes in transit time, quantitative estimates of malabsorbed carbohydrate would be inherently uninterpretable; (2) If a non-absorbable sugar such as lactulose is used for comparison, the interpretation of the  $H_2$  evolution following more complex meals or sugars (as – for example, starch) would be invalid because of the generally more prolonged oro-caecal transit times of the latter.<sup>18</sup>

The influence of the OCTT *per se* on the  $H_2$  excretion subsequent to carbohydrate malabsorption has, however, not been studied earlier.

It has been observed that delayed gastric emptying of lactulose due to addition of glucose does not affect the AUC's of the corresponding  $H_2$  excretion curves.<sup>19</sup> The effect of both metoclopramide and diphenoxylate on OCTT as observed by us is probably mainly on small intestinal transit.<sup>20,21</sup> Our results are not necessarily in conflict with the findings of

Read *et al*<sup>9</sup> that different colonic entry rates of carbohydrate may affect the timing and the magnitude of the peak H<sub>2</sub> production. It was shown<sup>9</sup> that fast colonic infusion of lactulose produced a greater H<sub>2</sub> response than slow infusion of the same dose. However, the difference in infusion rates used (7.5 times) was rather great, and AUC's were not compared. Furthermore, the OCTT's and the colonic entry rates of malabsorbed carbohydrate are not necessarily correlated,<sup>22</sup> and it is conceivable that substances with greatly different ileal emptying rates may provoke different H<sub>2</sub> responses. In a recent study,<sup>23</sup> however, a good correspondence was found between the H<sub>2</sub> production produced by ingestion of lactulose and infusion of starch.

Breath H<sub>2</sub> tests have been used to investigate the effect of drugs on upper intestinal transit.<sup>24,25</sup> The present study confirms earlier observations supporting the validity of using breath H<sub>2</sub> tests for this purpose.<sup>26</sup> Our findings may furthermore support the use of breath H<sub>2</sub> tests for evaluation of drugs influencing *both* intestinal absorption *and* upper intestinal transit time.

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