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Assessment of the reproducibility of the lactulose H_2 breath test as a measure of mouth to caecum transit time

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SUMMARY The lactulose H_2 breath test is in use as a simple non-invasive measurement of mouth to caecum transit time, but its reproducibility has never been assessed. We have examined the reproducibility of mouth to caecum transit time in 21 normal subjects using lactulose 10, 15, and 20 g; seven subjects being studied with 10 g and 12 each with 15 and 20 g doses. Transit time decreased with increasing doses of lactulose although the differences were not significant between or within (n=5) individuals. Variation in transit times between individuals was considerable with all doses of lactulose (mean coefficient of variation of 18·5, 29·7 and 28·3% with 10, 15, and 20 g respectively). The addition of lactulose to a liquid meal containing carbohydrate, fat, and protein decreased the coefficient of variation to <10% in four subjects studied. The lactulose H_2 breath test could be made more reproducible by including a liquid meal.

The study of gastrointestinal motility in man has been hampered by the complicated and invasive methods needed to measure smooth muscle activity and transit. The lactulose-hydrogen (H_2) breath test seemed therefore a suitable method for measurement of mouth to caecum transit time. In normal individuals H_2 is produced by bacterial breakdown of unabsorbed carbohydrate in the colon and excreted in measurable quantities in the breath.[1] Bond and Levitt[2] have shown that pulmonary excretion of H_2 occurred within 10 minutes after introduction of carbohydrate into the caecum and could thus be used to time mouth to caecum transit. They reported that transit times varied considerably between subjects, but within subject reproducibility was good, though the number studied was small. The development of a simple method of end expiratory sampling[3] had led to widespread use of this technique for studying small intestinal transit. More recent data, however, suggest that the factors on which the validity of the test is based might vary considerably in individuals. The colonic bacterial flora necessary for liberation of H_2 can change after laxatives and many antibiotics, thus affecting breath H_2 excretion.[4] Emotional stress affects the concentration and appearance time of H_2 in the breath.[5] More recently, sporadic small intestinal electric and motor activity, which was recorded in fasted animals,[6] has also been shown in man.[7] This interdigestive motor complex can affect small bowel transit and cause considerable variation in intestinal absorption of carbohydrate.[8] The possibility that small intestinal motility might vary considerably in the fasted individual has led us to reassess the reproducibility of the lactulose H_2 breath test as a measure of mouth to caecum transit time in the fasted state and after a liquid meal.

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Methods

SUBJECTS

The 21 subjects studied were healthy volunteers. None had taken antibiotics, or suffered any gastrointestinal disorder in the two weeks before the study. Lactulose (Duphalac) 10, 15, and 20 g diluted with water 50, 75, or 100 ml respectively was used. The different volumes of water were used to maintain a constant concentration of lactulose as osmolarity is known to affect small bowel transit time. Each subject was studied on at least three occasions not less than one week apart with a given dose of lactulose. Five subjects repeated the series of tests with all three doses of lactulose. Four of the subjects were also studied after a liquid meal containing glucose 40 g, Casilan 15 g, and corn oil 18 g, made up to 270 ml with water, to which was

added 30 g of lactulose. Thirty grams of lactulose were added because it was felt that this might offset the dilutional factor of the meal as well as the expected delay in gastric emptying. To ensure that any effect of a liquid meal on transit time could not be attributed solely to the effect of the larger volume on gastric emptying, transit time was measured in three subjects after the ingestion of 30 g of lactulose in 270 ml of H_2O. Subjects were instructed to keep a record of their diet the day before each study and to avoid foods likely to generate H_2. All studies began between 0800 and 0900 hours after an overnight fast. End expiratory breath samples were collected into 60 ml syringes from a modified Haldane-Priestley tube.[3] After a fasting sample, the subject ingested the given dose of lactulose and end-expiratory breath was sampled at 10 minute intervals for three hours. The tests were conducted in a quiet environment and subjects were instructed to move about as little as possible. H_2 concentration in the end-expiratory samples was measured by gas chromatography (Gow-Mac Series 552-69 gas chromatograph) using a molecular sieve column type 5A, calibrated with a standard gas containing 4·5 μmol (100 ppm) of H_2 in nitrogen, the reproducibility of which has been shown.[3]

Mouth to caecum transit time was taken as the time of initial increase above fasting levels of 0·5 μmol (10 ppm) or more of H_2 where this increase was sustained. Results were analysed using Student's *t* test.

Results

Twenty-one subjects were studied. Seven (six men, one woman) took lactulose 10 g; 12 (eight men four women) took 15 g, and 12 (11 men, one woman) 20 g. Five subjects (four men, one woman) were studied with all three doses of lactulose. Four subjects (two men, two women) who were studied with lactulose 20 g were also studied with lactulose 30 g added to the liquid meal. The mean ages of the subjects were similar (Table 1).

Table 1 *Details of subjects in each study group*

	n	*Men*	*Women*	*Mean age (range, yr)*
Lactulose 10 g	7	6	1	27·8 (21–33)
Lactulose 15 g	12	8	4	28·5 (20–40)
Lactulose 20 g	12	11	1	26·6 (20–33)
Lactulose 10, 15, and 20 g	5	4	1	30·6 (27–33)
Lactulose 30 g with liquid meal	4	3	1	26·2 (21–33)

TRANSIT TIME WITH LACTULOSE 10 G

Six subjects were studied on three occasions and one four times (Table 2). In two (AKB and JC), a rise in breath H_2 was not detectable on single occasions. The mouth to caecum transit time was 93·9±9·6 minutes (mean ± SEM) with a range of 50–120 minutes. The mean variation in transit expressed as the coefficient of variation was 18·5±5·1% (mean ± SEM, range 5·9–40%).

TRANSIT TIME WITH LACTULOSE 15 G

Three subjects were studied on four occasions and the rest three times each (Table 2). There was no rise in the breath H_2 of one subject (AKB) during one of the tests. The mean transit time was 85·8±SEM 7·7 minutes (range 43·4–136·7 minutes). The mean coefficient of variation for individual transit times was 29·7±SEM 5·8% (range 4·2–79·4%).

TRANSIT TIME WITH LACTULOSE 20 G

Eleven subjects repeated the test three times and one (MRF) was studied on a fourth occasion: raised breath H_2 was not recorded in this subject in one experiment (Table 2). The mean transit time for the group was 73·6±SEM 5·4 minutes (range 53·3–116·7 minutes). The coefficient of variation for transit times in individual subjects ranged from 7·9 to 72·6% (mean 28·2±SEM 6·3%).

COMPARISON OF DIFFERENT DOSES OF LACTULOSE IN ALL SUBJECTS

The Figure shows the mean breath H_2 concentration in all the subjects after different doses of lactulose. As expected, H_2 excretion increased with the amount of substrate ingested. The differences after different doses of lactulose in mean total H_2 production calculated by measuring the area under the curves were not significant ($p>0·5$). Mean transit times diminished with increasing doses of lactulose, but because of the wide variation between individuals these differences were not significant ($p>0·05$). Increasing the dose of lactulose did not decrease variability of individual transit times, the mean coefficient of variation being greater with 15 and 20 g than with the 10 g dose, though the difference was not significant ($p>0·05$). The concentrations of H_2 produced by given doses of lactulose also varied in individuals. The four subjects who produced no H_2 on single occasions tended to produce smaller amounts of H_2 than other subjects in reponse to the same dose of lactulose.

COMPARISON OF DIFFERENT DOSES OF LACTULOSE IN FIVE SUBJECTS

To eliminate the effect of variation between

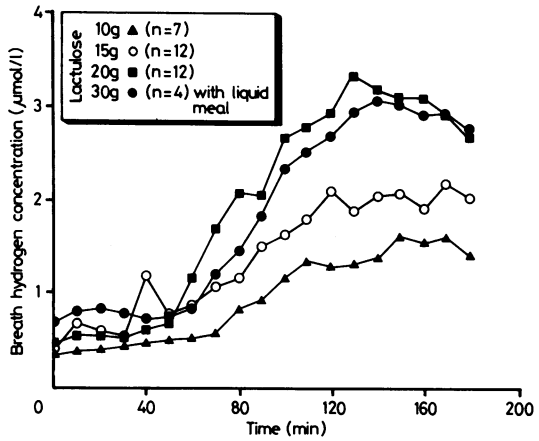

Fig. *Mean breath H_2 concentration (ppm) in all subjects studied with different doses of lactulose.*

individuals, five subjects (SLB, PJM, AKB, AA, and RW) were studied with all three doses of lactulose. Mean transit times with 15 and 20 g lactulose were similar (79·32 and 78·68 minutes respectively) and shorter than after 10 g (97·16 minutes) though the difference was not significant ($p>0·1$). Similarly, increasing the dose of lactulose had no effect on the coefficient of variation of individual transits.

EFFECT OF A LIQUID MEAL ON TRANSIT TIME

Four subjects (SLB, AKB, MRF, and IB) who had taken lactulose 20 g were also studied with lactulose 30 g taken together with the liquid meal containing absorbable carbohydrate (glucose), fat, and protein. The mean transit time was longer (82·5±SEM 8·7 minutes) than with lactulose 20 g in the fasted state (76·7±SEM 6·8 minutes) but not significantly so

Table 2 *Mouth to caecum transit times in subjects studied with different doses of lactulose*

		Transit time (min)				*Mean transit time (min)*	*Coefficient of variation (%)*
	Subjects	*Test 1*	*Test 2*	*Test 3*	*Test 4*		
Lactulose 10 g	SLB	60	80	80	130	88	34·1
	PJM	110	120	130		120	8·3
	AKB	*	100	130		115	18·4
	AA	100	110	130		113	13·5
	RW	30	50	70		50	40·0
	JC	80	70	*		75	9·4
	DB	100	90	100		97	5·9
Lactulose 15 g	SLB	70	100	130		100	30·0
	PJM	90	100	120		103	14·7
	AKB	60	70	*	90	73	20·9
	AA	40	70	70	110	73	39·6
	RW	30	40	40	80	48	46·7
	FM	80	110	150		113	31·0
	KS	30	40	60		43	35·3
	MT	60	70	90		73	20·1
	BY	70	70	110		83	27·7
	JPS	80	80	90		83	6·9
	DW	10	130	160		100	79·4
	JC	130	140	140		137	4·2
Lactulose 20 g	SLB	60	70	80		70	14·2
	PJM	160	110	80		117	34·6
	AKB	170	30	90		97	72·6
	AA	50	50	60		53	10·8
	RW	30	40	100		57	66·8
	FM	60	70	90		73	20·8
	MRF	*	70	80	70	73	7·9
	CW	60	70	60		63	9·1
	AH	50	60	90		67	31·2
	DW	70	90	110		90	22·2
	JS	50	60	60		57	10·2
	IB	40	70	90		67	37·7
Lactulose 30 g with liquid meal	SLB	80	80	90		83	6·9
	AKB	70	70	80		73	7·9
	IB	60	70	70		67	8·6
	MRF	100	110	110		107	5·4
Lactulose 30 g with water	SLB	70	90	110		90	23·5
	AKB	120	80	70		90	29·4
	MRF	60	90	100		83	25·1

* No rise in breath H_2 concentration after lactulose.

($p>0·1$). The coefficient of variation, however, was <10% in all individuals after the meal. This decrease did not achieve significance ($p>0·05$) when compared with variation in transit time after lactulose alone, probably because of the small number of subjects studied. None of the subjects found the liquid meal more unpalatable than lactulose alone. When 30 g of lactulose in 270 ml of water was studied in three subjects (SLB, AKB, and MRF) the mean transit time was similar 87·8±SEM 6·6 minutes) but the coefficient of variation was as great as for the other doses of lactulose.

Discussion

The rate of transit through the small bowel is important because of its effect on absorption. The effects of food[9] and disease[10] on small bowel transit have been studied using the lactulose H_2 breath test. The validity of the test rests on its reproducibility and this has never before been extensively assessed. Our results show that the variation in small bowel transit can be as great in the same individual as between individuals in the fasted state and the results of replicate experiments are therefore poorly reproducible. The most likely reason for this is the interdigestive activity front that occurs in the small intestine.[7] Motilin[11] and somatostatin[12] have been shown to affect this sporadic motility, but how it is initiated is unknown. Feeding has been shown to abolish the interdigestive motility pattern[13] and we therefore studied the effect of a liquid meal on the mouth to caecum transit time. Although only four subjects were studied, the coefficient of variation was less than 10% in all of them, whereas with lactulose alone it ranged from 7·9 to 72·6% even when the volume ingested was increased to 300 ml. This suggests that the measurement of intestinal transit with this technique should be more reproducible by including a liquid meal in the test. We have confirmed the observation of Bond and Levitt[2] that increasing the dose of lactulose shortens transit time, but after the doses of lactulose used in this study the within subject differences were not statistically significant. Neither did the different doses of lactulose affect significantly the variation of transit times between subjects. As expected, increasing the dose of lactulose increased excretion of H_2. Individual H_2 excretion rate differed, however, and low H_2 producers on occasion excreted no H_2 at all in expired air after lactulose. It has been suggested the population may be divided into H_2 and non-H_2 producers, the latter comprising <5%.[2] Our results indicate the existence of an intermediate group, who are occasional non-producers of H_2. This could be because they harbour only small numbers of H_2-producing bacteria in the colon, which, with the normal shifts of bacterial flora, become depleted at times.

This study has shown that the lactulose H_2 breath test in its present form is not reproducible in, or between, individuals, probably because of variations of small bowel motility in the fasted state. Our results suggest that better reproducibility can be achieved by the combination of lactulose with a liquid meal and that the test should be modified accordingly.

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