

Original articles

Intestinal permeability and oro-caecal transit time in elderly patients with Parkinson's disease

Keren N Davies, Debra King, David Billington, JA Barrett

Summary

The aetiology of weight loss in patients with Parkinson's disease is likely to be multifactorial. We studied 15 patients with Parkinson's disease and 15 age- and sex-matched controls and looked for evidence of malabsorption due to small bowel bacterial overgrowth or alteration of intestinal permeability. There was a marked increase in oro-caecal transit time in the patients with Parkinson's disease, although lactulose hydrogen breath testing did not show evidence of small bowel bacterial contamination. Intestinal permeability measured by the differential sugar absorption test was also deranged. There was reduced absorption of mannitol in patients with Parkinson's disease while lactulose absorption was similar in both groups, suggesting decreased non-mediated uptake across the enterocyte brush border membrane in patients with Parkinson's disease.

Keywords: intestinal permeability, sugar absorption, Parkinson's disease, bacterial overgrowth, nutrition, elderly

Weight loss is a frequent finding in elderly patients with Parkinson's disease,^{1–3} although the reasons have not been fully explained. An increase in energy expenditure has been shown in two studies^{1,2} whilst other possible contributing factors include dietary deficiency,³ or malabsorption due to small bowel bacterial overgrowth.^{4,5} We have previously shown that dietary deficiency is unlikely to be the cause.⁶ In this study of elderly patients with Parkinson's disease who had lost weight we looked for evidence of malabsorption, due to either small bowel bacterial overgrowth or changes in intestinal permeability. The lactulose hydrogen breath test has been shown to be a reliable measure of small bowel bacterial overgrowth and oro-caecal transit time.^{7–9} A differential sugar absorption test using mannitol and lactulose as probes was used to study intestinal permeability changes.^{10–12}

Methods**SUBJECTS**

Fifteen patients (nine women, median age 73.9 years, range 68.3–80.5) and 15 age- and sex-matched controls (median age 73.6 years, range 67.6–80.3) were studied. Ethical approval was

obtained from the Wirral Health Authority ethics committee. All subjects gave written informed consent.

The patients had a definite diagnosis of Parkinson's disease and a favourable response to L-dopa therapy. None of the patients were taking anticholinergic medications. Their condition and medication had been stable for at least six months prior to study. Patients with co-existing chronic diseases, eg, diabetes, or with known gastrointestinal disease, were excluded. All controls were screened, healthy elderly people.

All subjects gave a full medical history, underwent physical examination and a lactulose hydrogen breath test. On a separate occasion at least one week later, the differential sugar absorption test was performed. Parkinson's disease was graded using the Hoehn and Yahr scale¹³ and the Nottingham activities of daily living (ADL) scale¹⁴ was completed for each patient. Disease duration and total daily dose of L-dopa was recorded for each patient.

PROCEDURE*Lactulose hydrogen breath test*

Laxatives were discontinued for 48 hours prior to the procedure. All subjects were studied after an overnight fast having been asked to avoid foods likely to generate hydrogen for the 24 hours prior to the test. None had received antibiotics for at least two months and patients were asked to refrain from smoking on the morning of the test. Lactulose (10 g) was ingested with 50 ml of water and end expiratory samples of breath analysed for hydrogen content before and at 5-minute intervals for 30 minutes and every 15 minutes for a further 150 minutes after. End expiratory breath was analysed using an EC60 electrochemical hydrogen sensor (Bedfont Sittingbourne, Kent). The test duration was 180 minutes. Oro-caecal transit time was defined as the time between ingestion of the lactulose and the first definite and sustained rise in breath hydrogen.^{8,9} In practice, a rise of at least 5 ppm above fasting levels in the end expiratory hydrogen concentration was taken as the transit time. An early rise in breath hydrogen followed by a fall and later rise signifies bacterial overgrowth in the small intestine.^{7–9}

Differential sugar absorption test

A lactulose/mannitol differential sugar absorption test was performed. The amount of man-

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nitro recovered in urine in normal subjects is 40–100 times greater than the amount of lactulose recovered, as normal subjects absorb less than 1% of the lactulose administered. If intestinal permeability is abnormal there is an alteration in the amount of the sugars absorbed. Expressing the percentage urinary recovery of lactulose as a ratio of that of mannitol eliminates the effects of variability in absorption due to delayed gastric emptying or transit time through the intestine. Such effects would invalidate permeability tests using a single probe molecule. In addition, the differential sugar absorption test remains valid in the presence of renal impairment and does not depend on the accuracy of urine collection.

A sample of urine was collected after an overnight fast. Subjects swallowed a mixture of 5 g of lactulose, 2 g of mannitol and 22.3 g of glucose (as an osmotic filler) in 100 ml of water. Urine was collected for the next five hours into a container to which 1 ml of 20% (w/v) chlorhexidine was added as preservative. The volume was recorded prior to storing a small sample (10 ml) at -20°C until analysis. Subjects fasted throughout the test but were allowed to drink up to 250 ml of water two hours after ingestion of the sugars.

Analytical methods

Mannitol in urine was estimated as its trimethylsilyl derivative by gas liquid chromatography using alpha-methylglucose as internal standard.¹⁵ A Pye-Unicam gas chromatograph fitted with flame ionisation detectors and linked to a Pye-Unicam PU 4810 computing integrator was used. The column (2 m, 3 mm internal diameter) used was 10% OU17 or gas-chrom Q and column conditions were as follows: oven temperature 190°C , injector temperature 210°C , detector temperature 350°C , carrier gas (nitrogen) flow rate 40 ml/min. Lactulose in urine was determined by enzymic hydrolysis to fructose and galactose by beta-galactosidase followed by detection of fructose by a NADP⁺-linked spectrophotometric assay.¹⁶

Statistical methods

Data are described as median (range) percentage recoveries of each probe sugar in a five hour urine collection. Statistical analysis was performed with Mann-Whitney U test, Chi-square and Spearman's rank correlation (r_s) where appropriate. A p-value of 0.05 was considered significant.

Results

The patients had a mean disease duration of six (1–16) years and a mean daily dose of L-dopa of 450 (150–1250) mg. There was a significant correlation between total daily dose of L-dopa and disease duration ($r_s = 0.59$, $p = 0.01$). Disease severity varied between Hoehn and Yahr grades 1 and 5 and the Nottingham ADL score between 3 and 10. There was no significant correlation of Hoehn and Yahr grade with ADL score.

All of the Parkinson's disease patients and

controls had plasma urea and creatinine levels within the normal laboratory limits. There was no correlation between the urea ($r_s = 0.3$, $p = \text{ns}$) or creatinine ($r_s = 0.4$, $p = \text{ns}$) and the percentage mannitol excretion.

Ten of the 15 patients with Parkinson's disease had oro-caecal transit times greater than 180 minutes compared with three of 15 controls ($X^2 = 4.89$, $p = 0.03$). No subjects showed an early rise in breath hydrogen, suggesting that small bowel bacterial overgrowth was absent.

The percentage of mannitol recovered in the urine of the Parkinson's disease patients was significantly less than in the controls (11.72% (2.18–20.44) vs 16.16% (7.0–50.5), $p = 0.005$) (figure 1). Lactulose recovery was similar in the two groups (0.27% (0.03–0.43) vs 0.25% (0–1.11), $p = \text{NS}$). The lactulose:mannitol ratio was significantly higher in the patient group (0.024 (0.007–0.071) vs 0.012 (0.0–0.038), $p = 0.02$) (figure 2). There was no correlation between the lactulose:mannitol ratios and weight loss, Hoehn and Yahr score or ADL score for the Parkinson's disease patients. There was no correlation between the percen-

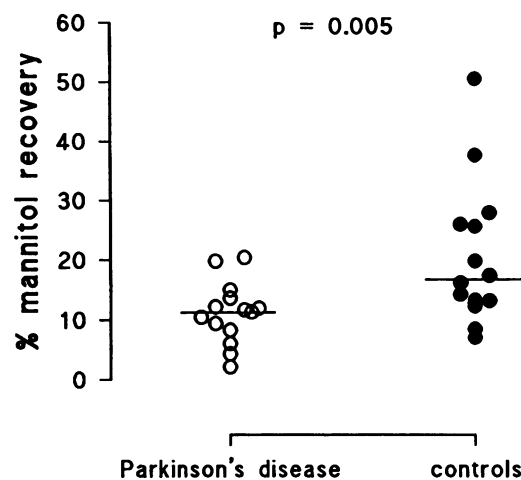


Figure 1 Percentage mannitol recovery in Parkinson disease patients versus control subjects

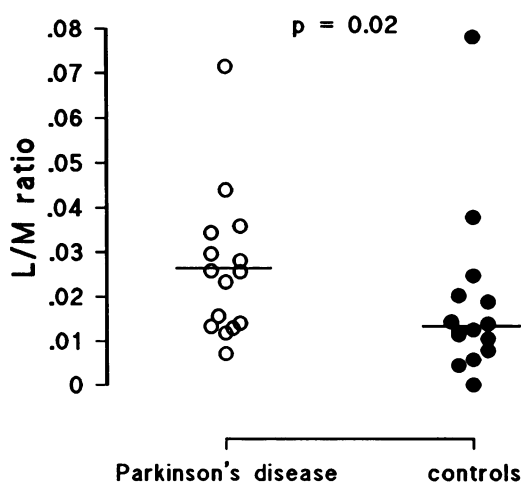


Figure 2 Lactulose/mannitol (L/M) ratio at five hours post-ingestion for patients with Parkinson's disease ($n = 15$) and age/sex matched controls ($n = 15$)

tage of lactulose or mannitol recovered in the urine and the oro-caecal transit time in either group.

Discussion

In this study of Parkinson's disease patients we have demonstrated two abnormalities of gastrointestinal function by using non-invasive screening tests. Firstly, a significantly prolonged oro-caecal transit time was found in patients with Parkinson's disease compared to healthy elderly subjects. The prolongation of the oro-caecal transit time was not related to disease severity or duration. The difference between the groups agrees with the findings of Piccione *et al*,¹⁷ who showed that oro-caecal transit time does not increase with age alone and is in contrast to those of Haboubi *et al*,¹⁸ who suggested age was a significant cause of a prolonged oro-caecal transit time. Secondly, we found that there was reduced absorption of mannitol with an increase in the lactulose:mannitol ratio, suggesting there is a reduction in the absorptive surface area of the small intestine.^{11,12,19} A number of studies have suggested small bowel bacterial overgrowth may be implicated in malabsorption in elderly subjects, even when the small bowel is anatomically normal,^{4,5,20} while Lipski *et al*, have suggested small bowel bacterial contamination results from ageing alone.²¹ Sampling of intestinal contents is an invasive technique which is unacceptable to patients, especially those disabled by diseases such as Parkinson's disease. The lactulose hydrogen breath test has been shown to be a good indirect test for small bowel colonisation⁸ and is non-invasive, inexpensive and acceptable to patients.^{8,20} Gastrointestinal hypomotility may be a significant cause⁷ and although we demonstrated prolonged transit times in the Parkinson's disease patients we did not find any evidence of small bowel bacterial contamination. The reason for the prolonged oro-caecal transit time is uncertain but may be due to disordered gastrointestinal autonomic function.^{22,23} Oesophageal dysmotility²² and prolongation of the colonic transit time²³ have been demonstrated in Parkinson's disease. Age alone is not responsible for these changes.²⁴ Lewy body lesions, the pathognomonic lesion of Parkinson's disease, have been identified in the ganglia of the sympathetic vertebral chain and in the ganglion coeliacum of patients with Parkinson's disease.^{25,26} Therefore autonomic or enteric²⁷ nervous system dysfunction may be responsible for the prolongation of the oro-caecal transit time.

The differential sugar absorption test is a non-invasive technique for investigating intes-

tinal permeability. It has been used to investigate a number of conditions, particularly coeliac disease.^{10-12,28,29} The reliability of the test has been demonstrated and it is a useful screening test prior to proceeding with more invasive investigations.^{12,30} In normal subjects monosaccharides such as mannitol are absorbed by non-mediated diffusion through small channels in the enterocyte brush border membrane. Disaccharides such as lactulose are excluded from these channels and are absorbed to a lesser extent, either across tight junctions between adjacent enterocytes or through extrusion zones at the tips of the villi.^{30,31} In elderly subjects the excretion of both sugars is reduced but the ratio of the sugars is not significantly different to young subjects and the test remains reliable in older subjects.³² The reduced absorption of monosaccharides is postulated to be due to a loss of absorptive surface area which is usually due to villous atrophy. The increased absorption of disaccharides is thought to be due to epithelial injury, increased shedding of cells at extrusion zones, or changes in the tight junction permeability.^{11,29,31}

We found that the Parkinson's disease patient group showed decreased urinary recovery of mannitol with normal recovery of lactulose. This excludes gross changes in absorptive surface area (eg, villous atrophy) since the urinary recovery of both sugars would be similarly decreased with a normal lactulose:mannitol ratio. Similarly, changes in oro-caecal transit time would be expected to affect the absorption of both sugars equally leaving the lactulose:mannitol ratio unaltered. The only explanation for the decreased mannitol recovery observed in this study is a specific alteration in the enterocyte brush border membrane. Several types of enteric disease,³³ together with enteropathogenic *Escherichia coli*,³⁴ cause atrophy of the brush border microvilli. Similar alterations in Parkinson's disease patients would be expected to decrease mannitol absorption whilst leaving that of lactulose unchanged, and may be one of the factors involved in under nutrition in Parkinson's disease. Alternatively, changes in the fluidity of the brush border membrane could produce similar results. Further investigation is required to confirm and explain these findings. This will require upper gastrointestinal endoscopy and examination of small intestinal biopsies by both light and electron microscopy.

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Methods of measuring transit time

- hydrogen breath test
- scintigraphy
- radio-opaque markers
- salazopyrine ingestion

Learning points

- patients with Parkinson's disease often lose weight
- the aetiology has not been fully elucidated
- dietary deficiency and malabsorption should be excluded
- an increase in energy expenditure is a contributory factor

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