Effects of α-glucosidase inhibitors on mouth to caecum transit time in humans

S D Ladas, A Frydas, A Papadopoulos, S A Raptis

Abstract
The α-glucosidase inhibitors acarbose and miglitol have been successfully used to control postprandial hyperglycaemia in diabetics. They probably work by slowing carbohydrate digestion and absorption, but their effect on mouth to caecum transit time has not been studied. The effect of acarbose (100 mg), miglitol (100 mg), and placebo on mouth to caecum transit time (380 kcal breakfast with 20 g of lactulose) was investigated in 18 normal volunteers using breath hydrogen analysis. Both miglitol and acarbose significantly increased breath hydrogen excretion (F2,34=6.31, p=0.005) and shortened the mouth to caecum transit time (F2,34=3.49, p=0.04) after breakfast compared with placebo. There was a significant negative correlation between breath hydrogen excretion and mouth to caecum transit time suggesting that with shorter transit times significantly more carbohydrates were spilled into the colon. These results indicate that α-glucosidase inhibitors accelerate mouth to caecum transit time by inducing carbohydrate malabsorption.

Methods
SUBJECTS
Eighteen healthy male volunteers aged 18-40 years (mean (SD) 30.3 (6.5) years) participated in the study. All were of normal body weight, taking a normal diet, and had a normal bowel habit. None had symptoms or a history of gastrointestinal disease or surgery or had received antibiotics in the two months before the study. Written informed consent was obtained from all individuals tested. The protocol of the study was approved by the Ethical Committee on Human Studies of the Department of Internal Medicine, University of Athens, in October 1985.

TEST MEAL
The breakfast used to measure MCTT consisted of two slices of toast (17 g), butter (15 g), marmalade (20 g), one hard boiled egg, and 200 ml of weak tea containing 20 g of lactulose (30 ml of Duphalac, Duphar, Southampton, UK) and 10 g of sucrose. The complete meal contained 380 kcal. Forty two per cent of the calories were derived from carbohydrate, 10% from protein, and 48% from fat. Since the prevalence of incomplete lactose digestion in Greece is 75%, milk was not included in the breakfast. The amount of lactose (2.4 g) contained in 30 ml of Dulphalac has been shown not to affect breath hydrogen excretion. This meal has been previously tested and proved to produce reproducible MCTT measurements.

MCTT AND CARBOHYDRATE ABSORPTION STUDY
These were investigated in a placebo controlled, double blind, randomised, three fold, cross over study with complete block design experiments. Each volunteer was studied three times. The washout periods were seven days. Acarbose (BAY g 5421) and miglitol (BAY m 1099) (Bayer AG, Leverkusen, Germany) were supplied as 100 mg tablets. The tablets and placebo were identical in size, shape, and colour and were distributed in cellophane bags labelled with each subjects random number and test day. The amount of lactose contained in the tablets was negligible (120 mg). They were swallowed half an hour before the ingestion of the test meal. After an overnight fast (10-12 hours), the volunteer consumed the test meal within 15 minutes. The breath hydrogen concentration...
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T=-6.68, excretion miglitol (100 mg), acarbose (100 mg), and placebo. Values of 18 normal volunteers are given as mean (SEM). Differences between treatment groups and placebo are significant (randomised blocks ANOVA, p<0.02-0.003).

Discussion
This is the first published report on the effects of α-glucosidase inhibitors on MCTT. Our results indicate that after ingestion of a solid-liquid meal (breakfast) miglitol and acarbose at a dose of 100 mg induce carbohydrate malabsorption and therefore shorten the MCTT. These results agree with those of a preliminary study of eight normal subjects given 200 mg of acarbose after a 380 kcal breakfast, where we had also observed a significant acceleration of MCTT in comparison with placebo. The negative correlation we have found between MCTT and breath H2 excretion suggests that with shorter transit times more carbohydrates are spilled into the colon. This is

CALCULATIONS AND STATISTICS
The area under the breath hydrogen curve was calculated using the trapezoid rule. Results in the text and figures are presented as mean (SEM). The statistical significance of the results was assessed by randomised blocks analysis of variance (ANOVA) and paired t test as appropriate. Correlation between breath hydrogen excretion and MCTT was evaluated by regression analysis and comparisons between slopes and correlation coefficients by covariance analysis. Probabilities of <0.05 were regarded as significant.

Results
All volunteers (n:18) ate the breakfast within 15 minutes and found it palatable. Non-hydrogen producers were not encountered in this study, since all volunteers excreted ≥20 ppm of breath hydrogen in at least one of the experiments after eating the breakfast marked with lactulose.

Treatment significantly affected MCTT (randomised blocks ANOVA: F2,34=3.49, p=0.042). This effect was due to the shorter MCTT after miglitol (107 (14) minutes) as well as after acarbose (106 (13) minutes) in comparison with placebo (139 (18) minutes), (paired t=2.16, p=0.023 and paired t=1.98, p=0.032 respectively).

The mean breath hydrogen curves after acarbose, miglitol, and placebo are shown in Figure 1. Significantly more hydrogen was excreted after acarbose (122-56 (14-67) or miglitol (112-67 (18-91)) than in placebo experiments (74-00 (11-40) ppm.4 hours, F2,34=6.31, p=0.005). When individual breath hydrogen excretion was plotted against MCTT (Fig 2), there was a significant negative log-linear correlation between the two variables after acarbose (Y=5.92-0.013x, r=-0.91, T=-8.75, p<0.001), miglitol (Y=5.83-0.013x, r=-0.86, T=-6.68, p=0.001), and placebo (Y=5.33-0.009x, r=-0.91, T=-9.02, p<0.001). The slopes of the regression lines, as well as the correlation coefficients of acarbose and placebo did not differ significantly (F1,32=3.57, F16,16=1.98, p=0.032 and respectively, p=0.023), nor did those of miglitol and placebo (F1,32=3.55, F16,16=2.07, p=0.10).

Figure 1: Breath hydrogen response to breakfast (380 kcal) marked with 20 g of lactulose after acarbose (100 mg), miglitol (100 mg), and placebo. Values of 18 normal volunteers are given as mean (SEM). Differences between treatment groups and placebo are significant (randomised blocks ANOVA, p<0.02-0.003).

Figure 2: Correlation of individual breath hydrogen excretion (log scale) and mouth to caecum transit time (MCTT) after ingestion of breakfast (380 kcal) marked with 20 g of lactulose. Correlations with regard to acarbose (100 mg), miglitol (100 mg), and placebo are significant (r=-0.91, r=-0.86, r=-0.91 respectively, p<0.001).
compatible with experiments in normal subjects ingesting increasing doses of lactulose, where an inverse relation between carbohydrate malabsorption and MCTT has been shown.\(^{18}\)

Though the inhibition of absorption induced by the \(\alpha\)-glucosidase inhibitors is the primary phenomenon, under the present experimental conditions, it is not possible to estimate whether the acceleration in the intestinal transit time contributes to carbohydrate malabsorption by reducing the contact time between the intestinal contents and small intestinal mucosa. However, it is known from ileal intubation studies that carborase may induce carbohydrate malabsorption of up to 50% of the ingested carbohydrate,\(^7\) and that glucose absorption is least efficient from the most rapidly moving front of an ingested bolus of glucose.\(^{19}\) Despite this evidence, one cannot preclude the possibility that the \(\alpha\)-glucosidase inhibitors produce their effect solely by inhibiting absorption and that the acceleration of MCTT is a secondary phenomenon, more or less irrelevant to the percent absorption. It may also be argued that the negative correlation we have found between breath \(H_2\) excretion and MCTT was due to the lactulose taken with the breakfast. However, Rumessen \textit{et al.} did not observe significant changes with regard to the area under breath \(H_2\) excretion curves, compared for the same dose of lactulose despite significant changes in MCTT induced by metoclopramide.\(^{18}\)

Studies published to date assume that \(\alpha\)-glucosidase inhibitors exert their control on postprandial hyperglycaemia by delaying carbohydrate absorption from the small intestinal lumen.\(^{4,9} \textit{et al.} \)\(^{19}\) However, as we have shown, \(\alpha\)-glucosidase inhibitors accelerate MCTT by inducing carbohydrate malabsorption. This unquestionable carbohydrate malabsorption,\(^7\) leads to a pronounced change in colonic function and metabolism by stimulating bacterial proliferation.\(^8,12\) Malabsorbed polysaccharides are fermented to short chain fatty acids which are rapidly absorbed from the colon in humans,\(^{23}\) providing 90–240 kcal/day in normal subjects – that is, 5–10% of daily energy requirements.\(^{24,25}\) Thus, in patients with carbohydrate malabsorption the colon may play an important role in meeting total energy needs. Furthermore, fermentation does not increase the colonic osmotic pressure and diarrhoea is not longer considered to occur as a side effect since most of this osmotic load is rapidly absorbed.\(^{20}\)

In conclusion, \(\alpha\)-glucosidase inhibitors, by inducing carbohydrate malabsorption, accelerate MCTT. We speculate that the beneficial effect on blood glucose concentrations of \(\alpha\)-glucosidase inhibitors, is mediated by small intestinal carbohydrate malabsorption, compensated by colonic short chain fatty acid absorption as an alternative source of energy.

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