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ORIGINAL PAPER

# The Effect of Oral α-Galactosidase on Intestinal Gas Production and Gas-Related Symptoms

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**Abstract** Bloating, abdominal distention, and flatulence represent very frequent complaints in functional disorders but their pathophysiology and treatment are largely unknown. Patients frequently associate these symptoms with excessive intestinal gas and the reduction of gas production may represent an effective strategy. The aim was to evaluate the effect of α-galactosidase administration, in a randomized double-blind placebo-controlled protocol, on intestinal gas production and gas-related symptoms after a challenge test meal in healthy volunteers. Eight healthy volunteers ingested 300 or 1200 GalU of α-galactosidase or placebo during a test meal containing 420 g of cooked beans. Breath hydrogen excretion and occurrence of bloating, abdominal pain, discomfort, flatulence, and diarrhea were measured for 8 hr. The administration of 1200 GalU of α-galactosidase induced a significant reduction of both breath hydrogen excretion and severity of flatulence. A reduction in severity was apparent for all considered symptoms, but both 300 and 1200 GalU induced a significant reduction in the total symptom score. α-Galactosidase reduced gas production following a meal rich in fermentable carbohydrates and may be helpful in patients with gas-related symptoms.

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## Introduction

Bloating, abdominal distention, and flatulence represent very frequent complaints in functional disorders [1]: the prevalence of functional abdominal bloating, for example, reaches 15% of community-based populations, with a female predominance [2, 3]. However, the mechanism responsible for their onset and the best treatment for their management are still largely not well defined. Patients very frequently associate the occurrence of these symptoms with an excessive amount of intestinal gas [4], though a clear interrelationship between them has been demonstrated only for flatulence [5]. It has, however, been shown that a subgroup of bloating patients is characterized by an increased production of gas [6], thus suggesting that this mechanism may also have a role in the pathophysiology of this very frequent symptom. The reduction of intestinal gas production may therefore represent an effective therapeutic strategy for the management of functional symptoms when their onset depends, at least in part, on gas hyperproduction.

Current therapeutic approaches are based on the administration of simethicone [7, 8], activated charcoal [9–12], a low-carbohydrate diet [13], and probiotics [14–17], but contradictory results are obtained. On the contrary, the use of antibiotics [6, 18] has produced encouraging results but the need for repeated treatment cycles requires a milder approach with less impact on the quality-quantity composition of intestinal bacterial flora.

In this framework, the breaking down of nonabsorbable oligosaccharides contained in legumes, fruit, and vegetables

**Table 1** Foods containing raffinose, stachyose, and verbascose

| |
|---|
| Cereals |
| Rice |
| Bran |
| Spelt |
| Maize |
| Oats |
| Barley |
| Muesli |
| Pulses |
| Beans |
| Chickpeas |
| Broad beans |
| Lentils |
| Peas |
| Soya |
| Fruit |
| Oranges |
| Bananas |
| Kiwi |
| Grapefruit |
| Nuts |
| Peanuts |
| Almonds |
| Hazel nuts |
| Walnuts |
| Pine nuts |
| Pistachios |
| Vegetables |
| Asparagus |
| Broccoli |
| Carrots |
| Cabbages |
| Cucumbers |
| Onions |
| Mushrooms |
| Potato |
| Leeks |
| Peppers |

before they can be metabolized by colonic bacteria may represent an alternative and actractive approach. The administration of $\alpha$-galactosidase, an enzyme with amylase-like activity, may be effective when some foods (Table 1) are ingested and the availability of two different oral formulations, in tablets and drops, facilitates its use. Using a double-blind, placebo-controlled, crossover protocol, we therefore evaluated the effect of $\alpha$-galactosidase administration on intestinal gas production and the occurrence and severity of gas-related symptoms after a meal rich in fermentable carbohydrates in healthy volunteers.

## Subjects and Methods

### Subjects

Eight healthy volunteers (four females; mean age, $31 \pm 3$ years; range, 26–34 years), members of the medical or paramedical staff, took part in the study. None of them had a history or symptoms of gastrointestinal disease. None had previously undergone therapeutic courses of antibiotics or drugs interfering with gut motility and sensitivity in the months preceding the study. All of them gave their informed consent and the protocol was approved by the local ethical committee.

### Methods

All the subjects underwent a preliminary evaluation of intestinal gas production capacity by breath $H_2$ excretion monitoring after the administration of 10 g lactulose. The presence of $H_2$ nonproducer status, defined as the absence of breath $H_2$ excretion $>20$ ppm higher than the fasting value after oral lactulose [19], was an exclusion criterion. $H_2$ production was therefore evident in all the enrolled subjects.

On 3 different days, separated by at least a week, 300 GalU (galactosidic units, i.e., the amount of enzyme releasing 1 $\mu$mol of galactose from the substrate in 1 min), 1200 GalU, or placebo was administered orally in a random order. In particular, to guarantee the blindness of the protocol, tablets containing 300 GalU of $\alpha$-galactosidase (Sinaire; Promefarm, Milan, Italy) or placebo were available, and on each occasion, subjects ingested four tablets containing 0 GalU (zero active + four placebo) or 300 GalU (one active + three placebo) or 1200 GalU (four active + zero placebo). Tablets were administered during a test meal consisting of 420 g of cooked beans (150 g of raw beans containing 0.84 g of raffinose, 2.94 g of stachyose, 3.78 g of verbascose), 50 g of white bread, 20 g of olive oil, 2 g of salt, and 300 ml of natural water, consisting of a total of 785 kcal. Breath $H_2$ excretion was then monitored for an 8-hr period. Occurrence and severity of bloating, abdominal pain, discomfort, flatulence and diarrhea were evaluated by visual analogue scale (VAS) [20] every 30 min for the 8-hr period. A mean score for each symptom and a mean total score combining scores for abdominal discomfort, pain bloating, and flatulence were also calculated. Moreover, the severity of flatulence was evaluated by inviting the subjects to record the number of flata occurring during the test.

### $H_2$ Breath Testing

In order to avoid prolonged intestinal gas production, due to the presence of nonabsorbable or slowly fermentable material in the colonic lumen, the evening before the test day, the

subject ate a meal consisting of only rice, meat, and olive oil [21]. This meal was then followed by a 12-hr fasting period. Breath testing started between 08:30 a.m. and 09:30 a.m., after thorough mouthwashing with 40 ml of 1% chlorhexidine solution [22]. Smoking [23] and physical exercise [24] were not allowed for 1 hr prior to and throughout the test.

Sampling of alveolar air was performed every 15 min by means of a commercial device (Gasampler; Quintron Instrument, Milwaukee, WI, USA) that allows the first 500 ml of deadspace air to be separated and discarded, while the remaining 700 ml of end-alveolar air is collected in a gas-tight bag. Subjects were instructed to avoid deep inspiration and not to hyperventilate before exhalation. A gas chromatograph dedicated to the detection of $H_2$ and $CH_4$ in air samples was used for breath sample analysis (Model DP12; Quintron Instrument). The accuracy of the detector was $\pm 2$ ppm, with a linear response range between 2 and 150 ppm $H_2$ and between 2 and 50 ppm $CH_4$.

For each patient, fasting breath $H_2$ excretion, peak breath $H_2$ excretion (calculated from the difference between the maximum value of $H_2$ excretion and the fasting value) and cumulative breath $H_2$ excretion, evaluated by means of an area under the time—concentration curve calculation [25], were recorded.

### Statistics

All variables are expressed as mean $\pm$ SD. All parameters showed a nonparametric distribution by Kolmogorov–Smirnov normality test. Kruskal–Wallis nonparametric analysis of variance and Dunn's test were used for comparison among the three treatment groups and multiple comparisons between pairs of groups, respectively. A $P$ value $<0.05$ was considered significant.

## Results

Figure 1 shows cumulative breath $H_2$ excretion after the two different doses of $\alpha$-galactosidase and placebo. Administration of 1200 GalU of $\alpha$-galactosidase induced a significant reduction in cumulative breath $H_2$ excretion compared to placebo ($P < 0.02$).

In Table 2, fasting and peak breath $H_2$ excretion values after $\alpha$-galactosidase or placebo are listed. Fasting breath $H_2$ excretion measured on each occasion showed similar results. There was no significant difference in peak breath $H_2$ excretion between any of the $\alpha$-galactosidase doses and placebo.

As far as symptom occurrence and severity during the 8-hr test period were concerned, in comparison with placebo, 1200 GaIU $\alpha$-galactosidase induced a significant reduction in the total number of flata (Fig. 2). A reduction in the number of flata was also evident after 300 GalU, but the difference was not significant. Mean scores for bloating, abdominal discomfort, and pain were all reduced after 300 and 1200 GaIU $\alpha$-galactosidase administration, but the differences did not reach statistical difference (Table 3). On the contrary, both 300 and 1200 GalU $\alpha$-galactosidase administration induced a significant reduction in total symptom score in comparison with placebo (Fig. 3).

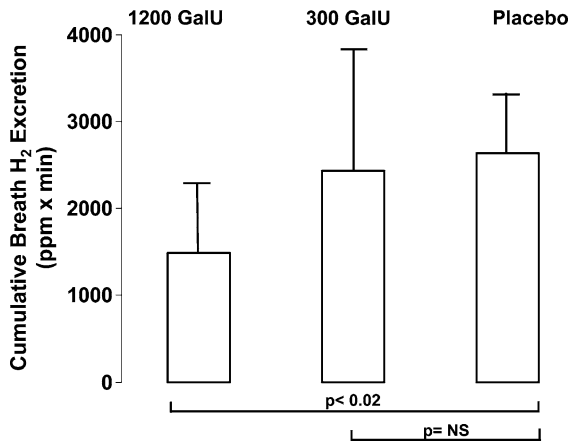


**Fig. 1** Cumulative breath $H_2$ excretion during the 8-hr test period after the administration of $\alpha$-galactosidase or placebo

## Discussion

This placebo-controlled study shows that $\alpha$-galactosidase at 1200 GaIU significantly reduces intestinal gas production, flatulence, and total symptom score in healthy volunteers and that the effect on symptoms is dose-related.

To date, various approaches based on different mechanisms have been tried for the treatment of gaseous symptoms, but a truly effective drug is still not available as symptoms may derive from different physiopatological mechanisms. Several recent papers by Malagelada and co-workers have shown that gas-related symptoms may be induced by gas retention at intestinal level [26, 27]. As a consequence, both increased gas elimination and suppression of production are considered primary targets for therapy. Simethicone and activated charcoal represent the drugs most frequently prescribed as a first line therapy. Activated charcoal acts through adsorbent properties [11, 12] while simethicone

**Table 2** Fasting and peak $H_2$ breath excretion after placebo and $\alpha$-galactosidase

| | Placebo | 300 GalU | 1200 GalU | $P$[a] |
|---|---|---|---|---|
| Fasting | $2 \pm 2$ | $3 \pm 3$ | $1 \pm 1$ | NS |
| Peak | $14 \pm 8$ | $18 \pm 10$ | $11 \pm 8$ | NS |

[a]Nonparametric ANOVA.

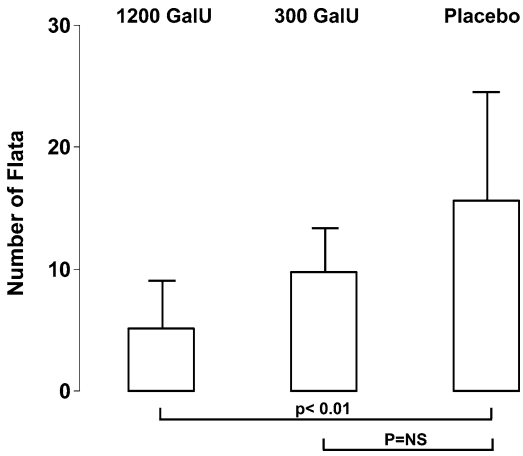


**Fig. 2** Total number of flata during the 8-hr test period after the administration of $\alpha$-galactosidase or placebo

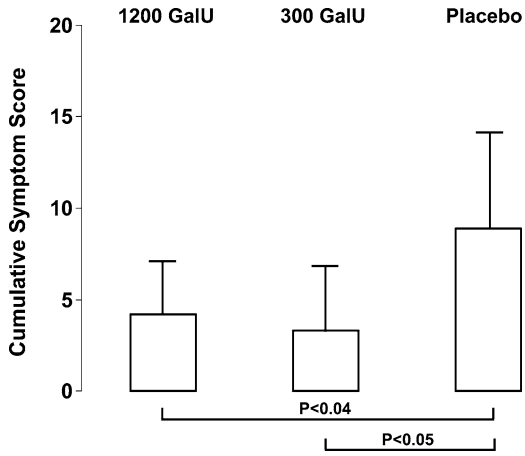


**Fig. 3** Total symptom score during the 8-hr test period after the administration of $\alpha$-galactosidase or placebo

decreases foaming [28] and accelerates the stomach-to-anus gas transit time [8]. Their action is therefore directed at facilitating elimination of already formed gas, but studies dealing with their use have provided inconsistent and contradictory results [7, 10–12]. In humans, an increase in gas propulsion was achieved experimentally by the use of neostigmine [29] and clinically by the use of tegaserod [30, 31]. However, tegaserod is not yet available in several countries, it is very expensive, and discontinuation of the therapy is very frequently accompanied by symptom recurrence [32].

The reduction of colonic fermentation could be achieved by the modification of bacterial flora by intestinal antibiotic (rifaximin) or probiotic administration [33]. They could be effective in functional patients or with small intestine bacterial overgrowth [6, 18]. Rifaximin induces a reduction in breath $H_2$ excretion [6, 18, 34, 36, 37], while probiotic administration does not modify intestinal gas production [14, 34, 35].

Low-carbohydrate dietary regimens have also been used, but poor compliance and the lack of a healthy diet limit this approach [13].

Carbohydrate intolerance, in particular, to nondigestible oligosaccharides, is a common cause of embarrassing gastrointestinal symptoms. While antiflatulants, prokinetic drugs, probiotics, and intestinal antibiotics can offer symptomatic relief, enzyme replacement therapy targets the cause of the problem, an enzyme deficiency.

The use of $\alpha$-galactoidase, an enzyme derived from the *Aspergillus niger* mold, determines the reduction of fermentable substrates by breaking down nonabsorbable oligosaccharides before they can be metabolized by colonic bacteria.

Our results show that in healthy volunteers the administration of $\alpha$-galactosidase significantly reduces intestinal gas production and symptom severity after a meal rich in fermentable carbohydrates. In particular, the high dose of 1200 GalU induced a significant reduction in intestinal gas production. Considering symptom severity, both doses induced a reduction in all evaluated symptoms, with a trend suggesting a dose-related effect. In comparison to placebo, the severity of flatulence was significantly lower after 1200 GalU, and both 1200 and 300 GalU induced a significant reduction of total symptom score. Thus, our results suggest that oral administration of $\alpha$-galactosidase may have a role in the management of intestinal gas production and, consequently, gas-related symptoms.

Our data agree with a previous paper adopting a similar protocol [38] in which acarbose was administered orally to induce an experimental model of carbohydrate malabsorption. The colonic delivering of malabsorbed carbohydrate induces a relevant increase in fermentation by colonic flora. Results of this study showed that $\alpha$-galactosidase significantly reduced flatulence score and breath hydrogen excretion with respect to placebo, thus suggesting an important effect on colonic fermentation.

A previous open trial [39], published only as a preliminary report, showed a dose-dependent effect of $\alpha$-galactosidase on severity of symptoms and breath $H_2$ excretion. The administration of 196, 391, and 2737 GalU induced a progressive reduction in the peak $H_2$ response and cumulative symptom

**Table 3** Severity of symptoms (VAS) after placebo and $\alpha$-galactosidase

| | Placebo | 300 GalU | 1200 GalU | $P$[a] |
|---|---|---|---|---|
| Bloating | $11 \pm 14$ | $5 \pm 9$ | $7 \pm 9$ | NS |
| Abdominal pain | $3 \pm 4$ | $1 \pm 1$ | $1 \pm 1$ | NS |
| Abdominal discomfort | $8 \pm 13$ | $2 \pm 3$ | $3 \pm 5$ | NS |
| Flatulence | $0.5 \pm 0.2$ | $0.3 \pm 0.3$ | $0.2 \pm 0.2$ | NS |
| Diarrhea | $0 \pm 0.5$ | $0.5 \pm 1$ | $0 \pm 0$ | NS |

[a]Nonparametric ANOVA.

index. Our results are in agreement with this study, but we were unable to show a dose-dependent effect on intestinal gas production. Another double-blind, placebo-controlled study showed that 8 drops of $\alpha$-galactosidase, the equivalent of approximately 240 GalU, significantly reduces flatulence with respect to placebo [40]. In our study a significant reduction of flatulence was evident only for a 5 $\times$ dose of enzyme, but major differences between the test meals may explain these discrepancies.

It is important to note that our results were obtained in healthy volunteers receiving a high amount of fermentable substrate and should not necessarily be considered valid for patients with functional gastrointestinal disorders. In these patients different pathophysiological mechanisms may be responsible for symptoms, including the presence of abnormal motility patterns involving both colon and small bowel [41], alterations of visceral sensitivity characterized by both hypersensitivity [42] and abdominal referral of visceral sensations [43–45], alterations of brain-gut interactions [46] or cerebral blood flow, suggestive of activation of different areas in the management of afferent fires [47], and autonomic dysfunction [48].

Our results support the use of $\alpha$-galactosidase for preventing increased gas production and gas-related symptoms and provide a rationale for the use of $\alpha$-galactosidase in IBS patients complaining of flatulence, bloating, and abdominal discomfort. This novel and promising approach warrants further investigation, especially in the subgroup of IBS patients in whom direct evidence of increased intestinal gas production, responsible for postprandial gas-related symptoms, is shown. Moreover, the reduction of colonic delivery of unabsorbed carbohydrates may improve abdominal symptoms either via a reduction of gas production or via an inhibition of the effects on colonic mucosa of other fermentation products, for example, short-chain fatty acids. It is known that an increased level of short-chain fatty acids in the right colon induces rapidly propagated, high-pressure waves propelling colonic content extremely effectively and resulting in both pain and diarrhea [49, 50]. Such high-amplitude wave motor activity may account for an increased parietal tension at the colonic level, causing, in turn, an increased firing of wall tension receptor, recently described as a pivotal step for mechanosensitivity of the colon [51]. Therefore, the positive effect of colonic fermentation reduction relies also on mechanisms other than a mere "bowel deflation."

In conclusion, oral $\alpha$-galactosidase tablets proved to be effective for controlling excessive gas production and preventing gas-related symptoms following a meal rich in fermentable carbohydrates. Its use is also supported by its recognized lack of toxicity, which makes it suitable for the target group of patients independently by their concomitant diseases and associated treatments.

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