Alpha-galactosidase versus active charcoal for improving sonographic visualization of abdominal organs in patients with excessive intestinal gas

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KEYWORDS

Abdominal
ultrasonography;
Active charcoal;
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Abstract *Background and aims:* Intestinal gas is a frequent cause of poor visualization during gastrointestinal ultrasound (US). The enzyme alpha-galactosidase may reduce intestinal gas production, thereby improving abdominal US visualization. We compared the efficacies of alpha-galactosidase and active charcoal in improving US visualization in patients with previous unsatisfactory abdominal US scans caused by excessive intestinal gas.

Materials and methods: 45 patients with poor visualization of at least one target organ: pancreas, hepatic lobes (score 0–2) or common bile duct (CBD) (score 0–1) were enrolled in a prospective randomized, crossover, observer-blinded study. The patients received alpha-galactosidase (Sinaire Forte, Promefarm, Milan, Italy) 600 GalU t.i.d. for 2 days before abdominal US plus 900 GalU the morning of exam or active charcoal 448 mg t.i.d., for 2 days before the exam plus 672 mg the morning of the exam. Visualization was graded as follows: 0 = none (complete gas interference); 1 = severe interference, 2 = moderate interference, 3 = mild interference; 4 = complete (no gas interference).

Results: 42 patients completed the study. Both alpha-galactosidase and active charcoal improved the visualization of target organs. Visualization of the right hepatic lobe, CBD and pancreatic tail was significantly improved (vs. baseline) only by alpha-galactosidase ($p < 0.01$). Scores ≥ 3 for all parts of the pancreas and both hepatic lobes were achieved in only 12.5% of the patients after both treatments. Both products were well tolerated.

Conclusion: Alpha-galactosidase and active charcoal can improve US visualization of abdominal organs in patients whose scans are frequently unsatisfactory due to excessive intestinal gas. Visualization of the pancreatic tail and right hepatic lobe was significantly improved only by alpha-galactosidase. However, both treatments allowed adequate visualization of all target organs during the same examination only in a few patients.

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Sommario *Background e scopi:* il gas intestinale è una causa frequente di scarsa visualizzazione degli organi addominali in ecografia gastrointestinale.

L'enzima alpha-galattosidasi potrebbe ridurre la produzione del gas intestinale, aumentando la visualizzazione ecografica dell'addome. Abbiamo confrontato l'azione dell'alpha-galattosidasi e del carbone attivo per aumentare la visualizzazione ecografica in pazienti con esami ecografici addominali precedentemente non adeguati a causa dell'eccessivo meteorismo.

Materiali e metodi: 45 pazienti con scarsa visualizzazione di almeno un organo target: pancreas, lobi epatici (punteggio 0–2) o del dotto biliare comune (CBD), sono entrati a far parte di uno studio prospettico randomizzato, crossover, in cieco.

I pazienti hanno ricevuto alpha-galattosidasi (Sinaire Forte® Promefarm, Milano, Italia) 600 GalU tre volte al giorno per 2 giorni prima e 900 GalU la mattina dell'esame, oppure carbone attivo 448 mg tre volte al giorno, nei 2 precedenti, più 672 mg la mattina dell'esame. La visualizzazione è stata classificata come segue: 0 = nessuna visualizzazione (interferenza gas completo); 1 = grave, 2 = moderato, 3 = lievi interferenze; 4 = visualizzazione completa (nessuna interferenza gas).

Risultati: 42 pazienti hanno completato lo studio. Sia l'alpha-galattosidasi che il carbone attivo migliorano la visualizzazione degli organi bersaglio. La visualizzazione del lobo epatico destro, del dotto biliare comune e della coda del pancreas è risultata significativamente migliorata solo con alpha-galattosidasi, rispetto al basale ($p < 0,01$). Buoni punteggi (≥ 3) in tutte le parti del pancreas e dei lobi epatici sono stati trovati solo nel 12,5% dei pazienti per entrambi i trattamenti. Entrambi i prodotti sono risultati ben tollerati.

Conclusione: l'alpha-galattosidasi e il carbone attivo possono migliorare l'ecografia nei pazienti con scansioni addominali precedentemente insoddisfacenti a causa di eccessivo meteorismo. La visualizzazione della coda del pancreas e del lobo epatico destro è risultata significativamente migliorata solamente con l'alpha-galattosidasi. Tuttavia, solo pochi pazienti possono avere una visualizzazione simultanea adeguata di tutti gli organi bersaglio.

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Introduction

Excessive intestinal gas is the most common cause of interference and poor visualization of abdominal organs during abdominal ultrasound (US). It is also a frequent and well-known cause of abdominal discomfort, which is sometimes severe enough to require instrumental investigation.

Poor ultrasonographic visualization of the splanchnic and retroperitoneal organs is often attributed to shadowing by gas in the colon. The mechanisms responsible for excessive gas production in the colon are not fully understood. However, several therapeutic approaches have been suggested to reduce it, including the administration of simethicone [1,2], activated charcoal [3–6], probiotics [7,8], and antibiotics [9]. Very few data are available on the efficacy of these drugs in the management of abdominal symptoms and in improving ultrasonographic visualization of abdominal organs, and those that are available are often contradictory [10–16].

Alpha-galactosidase has recently been shown to reduce gas production following a meal rich in fermentable carbohydrates, and it may be helpful in patients with gas-related symptoms [17–19]. Very small amounts of this enzyme are naturally present in a variety of fresh vegetables. It specifically breaks down nondigestible oligosaccharides (raffinose, stachyose, and verbascose) into monosaccharide components (glucose, galactose, sucrose, fructose) before they reach the colon and undergoes fermentation by the microbial flora of the intestine [17–19]. Therefore, the use of this enzyme may reduce the production of intestinal gas, thereby improving

the visualization of abdominal organs situated behind intestinal loops, such as the pancreas or in some cases the left and/or right hepatic lobes.

To date, no studies have been published on the efficacy of alpha-galactosidase in reducing intestinal gas and improving organ visualization during abdominal US. In the present study, we compared the efficacy of this enzyme with that of active charcoal in improving ultrasonographic visualization of the upper abdominal organs in patients with histories of unsatisfactory abdominal US scans caused by excessive intestinal gas.

Patients and methods

From June 2007 through December 2008, we conducted a randomized, double-blind, crossover study to compare the efficacies of alpha-galactosidase and active charcoal in improving sonographic visualization of abdominal structures. The study population included adult outpatients who were consecutively examined by our staff with abdominal ultrasonography and found to have intestinal gas that impaired US visualization of the upper abdominal organs. All of the enrolled patients also had one or more previous abdominal US scans that had also been judged incomplete due to gas-related interference. Active charcoal was chosen as the control treatment because it is widely used in Italy to reduce intestinal gas and to prepare patients for abdominal US exams. Like alpha-galactosidase, active charcoal mainly targets gas production in the colon, and the two agents are also similar in terms of the mode of administration.

Inclusion criteria were age ≥ 18 years, history of at least one previous unsatisfactory abdominal US scan caused by excessive intestinal gas, and a current US examination of upper abdomen in which at least one target organ was poorly and/or incompletely visualized because of the presence of air: pancreas (head, body, tail); hepatic lobes (with score 0–2, see later [15]); common bile duct (CBD) (with score 0–1).

Exclusion criteria were obesity (defined as a body mass index [BMI] of >30 kg/m²), which can also impair sonographic visualization of abdominal structures; occasional (e.g., postprandial) rather than constant presence of abdominal gas; conditions that might change during the study period or that might preclude repeated follow-up US examinations (i.e., cirrhosis with ascites, malignancies involving an abdominal organ, severely active inflammatory bowel disease, Crohn's disease with complications such as strictures or abscesses; psychiatric disorders; or pregnancy); and refusal to undergo all US evaluations planned in the study. The study was approved by the institutional review board of the L. Sacco University Hospital in Milan, and written, informed consent was obtained from all patients who agreed to participate in the study.

Eligible patients received the study and control treatments in random order established with a computer-based list. The study regimen consisted of alpha-galactosidase 300 GalU (Sinaire Forte, Promefarm S.r.l., Milan, Italy), 2 tablets 3 times a day for the two days preceding the ultrasonographic examination plus 3 tablets (900 GalU) the morning of the examination. The control treatment consisted of active charcoal (Carbone Vegetale, Marco Viti Farmaceutici, Milan, Italy) at a dose of two 224-mg tablets 3 times a day for the two days preceding the ultrasonographic examination plus 3 tablets the morning of the US examination. For each patient, the second US examination was scheduled 7 days after the first, at the same hour of the day, to allow an adequate wash-out period between the two treatments. During the two days preceding each examination, the patients were instructed to maintain their normal dietary habits, avoid chewing gum, and take nothing by mouth (other than the final dose of the treatment agent) for the 8 h preceding the examination.

The study was performed in an investigator-blinded manner. Supplies of study vs. control drugs were randomly distributed to the patients by the same physician (E.R.), and patients were aware of the study preparation they were receiving. The US examinations were performed by the same investigator (G.M.), who was not aware of the product used by the patient before the examination. All examinations were performed in the same manner with a Hitachi Logos HiVision C scanner equipped with a high-resolution broadband convex probe (4–7.5 MHz). During each examination, target organs were scanned with patients in various positions (supine, left lateral decubitus, and seated, if necessary). A video-clip from each target organ was taken at the baseline examination and at each of the post-treatment examinations.

Assessment of gas interference during US

Visualization of the head, body, and tail of the pancreas, the left and right hepatic lobes, and the CBD were rated with the following scale, as previously reported [15]:

0 = no visualization (large amount of gas producing complete interference);

1 = visualization of a small part of the organ (large amount of gas with interference);

2 = fair visualization of most of the organ but with interference of gas (moderate amount of gas with interference);

3 = visualization of most but not all of the organ (small amount of gas with mild interference);

4 = complete, good visualization of the organ (little or no gas, no interference).

In this study, we did not compare the accuracy of US in characterizing hepatic or pancreatic lesions with that of computed tomography or magnetic resonance imaging nor did we assess the impact of US with bowel preparation on patient management.

Along with assessment of gas interference during US, all symptoms experienced by patients during each treatment were reported, and patient compliance was verified by questionnaire.

Statistical analysis

The sample size was calculated to achieve 80% power with a 5% probability of type I error. Based on estimated rates of pancreatic visualization scores of ≥ 3 (65% and 90% for control and test treatments, respectively), we determined that a sample of 43 patients would be needed to show that the test preparation was significantly more effective than the standard treatment. No carryover effect was anticipated, and responses to the two preparations were assumed to be independent. To compensate for minor deviations from the latter two assumptions, we increased the number of patients in the target sample to 45.

The McNemar and Fisher exact tests were used to compare baseline data and that obtained after each of the two treatments. A p -value < 0.05 was considered statistically significant.

Results

Of the 45 patients originally enrolled in the study, 42 (93%) (30 men, 12 women; age range: 31–78 years, mean age 57 ± 14 years) completed the study. Their characteristics (smoking status, reasons for abdominal US) are shown in Table 1. Their body mass index (BMI) (mean $\pm$ s.e.) was 24.9 ± 2.2 .

At baseline, the head and tail of the pancreas and the common bile duct were satisfactorily visualized (scores of 3–4) in no more than one third of the patients. The right and left lobes of the liver were visualized well in 60% and 80% of the patients, respectively.

Both alpha-galactosidase and active charcoal improved the visualization of all target organs.

In particular, the percentages of patients with satisfactory (scores of ≥ 3) visualization of the head, body, and tail of the pancreas increased from baseline values of 32.5%, 70%, and 10%, respectively, to 75%, 87.5%, and 37.5% after alpha-galactosidase and to 80%, 92.5%, and 20% after active charcoal. Rates of satisfactory (≥ 3) visualization of the liver also increased from 80% (left lobe) and 60% (right

Table 1 Clinical data of the study population.

Clinical features	No. patients
Smoking status	
Current smokers	7
Nonsmokers or ex-smokers	35
Reason for US	
Recurrent dyspeptic symptoms/ abdominal complaints	9
Increased ALT levels	2
Follow-up of steatohepatitis, viral hepatitis, or cirrhosis	10
Follow-up of focal hepatic lesions	13
Follow-up of gallbladder polyps/stones	1
Follow-up of neoplastic disease	7

lobe) at baseline to 87.5% and 82.5% after alpha-galactosidase and to 87.5% and 72.5% after active charcoal. Examples of the improved visualization of the right lobe of the liver and the pancreatic body are shown in Figs. 1 and 2, respectively.

The CBD was completely visualized in 10% of the patients at baseline and in 32.5% and 25% of the patients after alpha-galactosidase and active charcoal, respectively.

Considering all target organs as a whole, the improved visualization produced by alpha-galactosidase was not significantly different from that achieved with active charcoal ($p > 0.09$). However, for the right hepatic lobe, the CBD, and the tail of the pancreas, significantly improved visualization (versus baseline) was achieved only after alpha-galactosidase treatment (Table 2).

Although both agents improved visualization of target organs, only 12.5% of the examinations performed after control or study preparation included adequate scores (>2) for all parts of the pancreas and liver.

Visualization scores for patients with normal and high BMIs (>25) were not significantly different at baseline, after alpha-galactosidase, or after active charcoal treatment.

Compliance with both treatment protocols was excellent. A total of 7 adverse events were reported: mild constipation and diarrhea (reported by 2 patients during both treatments), moderate abdominal pain (reported by 1 patient during alpha-galactosidase treatment), and moderate constipation (reported by 2 patients taking active charcoal). Seventy-two percent of the patients had dyspepsia or abdominal complaints at baseline, and improvement of gas-related symptoms was reported by 66% of the patients during treatment with alpha-galactosidase and by 34% during active charcoal treatment.

Figure 1 (a) Baseline sonogram: Oblique view of the right lobe of the liver, which is partially obscured by gas in the colon. Oblique sonograms of the same region obtained after treatment with active charcoal (b) and alpha-galactosidase (c). (G: Gallbladder).

Figure 2 (a) Baseline sonogram: Transverse scan of the pancreas with poor visualization of the pancreatic body. Transverse sonograms obtained after active charcoal (b) and alpha-galactosidase (c). (P: Pancreas).

Discussion

This study showed that alpha-galactosidase and active charcoal can both improve the US visualization of abdominal organs in patients who have experienced repeated unsatisfactory abdominal US scans caused by excessive presence of intestinal gas. In these patients, both treatments allowed complete or almost complete visualization of the liver, head and body of pancreas in over 75–80% of patients. In contrast, the common bile duct and the tail of

the pancreas, which were initially well visualized in only 10% of the cases, were satisfactorily visualized in 32.5% and 37.5% of the patients after treatment with alpha-galactosidase and in 25% and 20% after active charcoal.

The efficacies of the two treatments in improving target organ visualization were not significantly different. Significant improvement with respect to baseline was obtained with alpha-galactosidase for visualization of the pancreas, right hepatic lobe, and CBD, whereas active charcoal significantly improved only visualization of the head and

Table 2 Number of patients (%)^a with adequate visualization scores (3 or 4) for each target organ at baseline and after each treatment.

	Baseline	Alpha-galactosidase		Active charcoal	
	No. (%)	No. (%)	<i>p</i> -value ^b	No. (%)	<i>p</i> -value ^b
Pancreas					
Head	13 (32.5%)	30 (75.0%)	0.000	32 (80.0%)	0.000
Body	28 (70.0%)	35 (87.5%)	0.004	37 (92.5%)	0.000
Tail	4 (10.0%)	15 (37.5%)	0.003	8 (20.0%)	0.125
Liver					
Left lobe	32 (80.0%)	35 (87.5%)	0.549	35 (87.5%)	0.453
Right lobe	24 (60.0%)	33 (82.5%)	0.022	29 (72.5%)	0.227
Common bile duct	4 (10.0%)	13 (32.5%)	0.012	10 (25.0%)	0.070

^a Results are shown for the 42 patients who completed the study.

^b Test versus baseline value.

body of the pancreas. This suggests that alpha-galactosidase may be somewhat superior to active charcoal (a difference that was not detected, probably owing to a type II error).

Increases in the rates of satisfactory visualization with alpha-galactosidase and active charcoal varied from organ to organ. The greatest improvement was seen in the assessment of the head of the pancreas (42.5–47.5%). Minimal increases were achieved for the left lobe of the liver (7.5%). For other target organs increases in the rates of satisfactory visualization did not exceed 27.5%.

Other studies have used simethicone, alone or with prokinetics or laxatives, to improve the quality of abdominal US, in particular for the visualization of the pancreatic head [11,13–15]. Lef-Toaff et al. reported that simethicone-coated cellulose improved visualization of the head and body of the pancreas in 61% of their patients and that of the pancreatic tail in 67% [14]. The same product also improved visualization of the pancreatic tail in the study by Abu-Yusef, where complete visualization of this structure was achieved in 79% of the patients treated with the simethicone-water-rotation technique [15]. Other randomized, double-blind, placebo-controlled studies showed that clebopride and simethicone were better than placebo in improving quality of ultrasonographic images [10,12,20]. In particular, Varas and Lopez found that visualization rates for the head and body of the pancreas increased from 4% to 42.8% in the placebo group and from 0% to 76% in those treated with simethicone plus clebopride. However, the same study failed to show any significant improvement in the visualization of the tail of the pancreas or the left kidney [20]. In another randomized, placebo-controlled trial, simethicone, alone or combined with senna, had no effect on the visibility of abdominal organs (pancreas, aorta, and left kidney) [11].

These results are quite difficult to compare because the studies differ in terms of the scoring systems used, the kind of patients and therapies examined, and the target organs considered. All of the studies investigated preparations that reduce air mainly in the stomach and upper digestive tract, and they all analyzed the visibility of retrogastric organs. In contrast, we compared two products with recognized effects on colonic gas production, and we considered only patients with documented histories of poor visibility on previous abdominal US examinations. In addition, we evaluated target organs like the liver and CBD, which have never been considered before. These factors might partly explain why our US visualization rates were somewhat lower than those achieved in earlier studies and why both treatments had limited impacts in terms of significantly improving the visibility of all target organs. Indeed, satisfactory visualization of all targets with a single examination was achieved in only 12.5% of the patients.

To our knowledge this is the first attempt to assess the efficacy of colon-targeted preparation for abdominal US in patients with excessive intestinal gas and the first demonstration of the potential usefulness of alpha-galactosidase in reducing abdominal gas. Our study has some limitations related to its design. For example, it was single- rather than double-blinded. Furthermore, it was not placebo-controlled. The control product was another drug commonly used for reducing colonic gas. The study also focused specifically on abdominal organs likely to be obscured by colonic gas, such as

the liver and pancreas, instead of all abdominal organs. Indeed, we assessed the right and left hepatic lobes, together with the pancreas and CBD, because the liver is frequently the main target organ of US follow-up for benign and malignant conditions (including focal lesions, hepatitis, cirrhosis, and intestinal or extraintestinal neoplastic disease). In most of these patients, excess bowel gas renders US an unsatisfactory tool for follow-up, and clinicians are forced to resort to more expensive and potentially dangerous imaging techniques that use ionizing radiation. Therefore, methods that safely and effectively reduce gas artifacts and improve the quality of US are especially useful in patients with excessive abdominal gas requiring repeated US follow-up examinations.

Although alpha-galactosidase and active charcoal both produced statistically significant improvement in abdominal organ visibility, it is still a matter of debate as to whether these results are sufficient to justify the time and cost of the preparation. Our results suggest that alpha-galactosidase, which can reduce colonic gas, might be combined with simethicone, which is mainly active on gastric gas, to further improve the visualization of some target organs in patients with excessive abdominal gas. We are aware that bowel preparation for US represents an added cost, but it might be offset to some extent by the improved US visualization of abdominal organs, which could reduce the demand for more costly imaging studies, such as computed tomography or magnetic resonance imaging, in particular for patients requiring long-term follow-up. However, this possibility needs to be evaluated in future studies.

Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary material

Supplementary data related to this article can be found online at [doi:10.1016/j.jus.2012.04.002](https://doi.org/10.1016/j.jus.2012.04.002).

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