ORIGINAL PAPERS

Lactose tolerance test shortened to 30 minutes: An exploratory study of its feasibility and impact

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ABSTRACT

Introduction: Lactose malabsorption (LM) is a very common condition with a high prevalence in our setting. Lactose tolerance test (LTT) is a basic, affordable test for diagnosis that requires no complex technology. It has been recently shown that this test can be shortened to 3 measurements (baseline, 30 min, 60 min) with no impact on final results. The purpose of our study was to assess the feasibility and benefits of LTT simplification and shortening to 30 min, as well as the financial impact entailed.

Material and methods: A multicenter, observational study of consecutive patients undergoing LTT for LM suspicion. Patients received 50 g of lactose following a fasting period of 12 h, and had blood collected from a vein at all 3 time points for the measurement of blood glucose (mg/dl). Differences between the shortened and complete test forms were analyzed using McNemar's test. A comparison of blood glucose levels between patients with normal and abnormal results was performed using Student's T-test for independent mean values. Consistency was assessed using the kappa index. A p < 0.05 was considered to be statistically significant.

Results: A total of 270 patients (69.6 % females) were included, with a mean age of 39.9 ± 16 years. LTT was abnormal for 151 patients (55.9 %). We observed no statistically significant differences in baseline blood glucose levels between patients with normal and abnormal LTT results (p = 0.13); however, as was to be expected, such differences were obvious for the remaining time points (p < 0.01). Deleting blood glucose measurements at 60 minutes only led to overdiagnose LM (false positive results) in 6 patients (2.22 %), with a kappa index of 0.95 (95 % CI: 0.92-0.99) (p < 0.001) *versus* the complete test. Suppressing measurements at 60 min would have saved at least € 7,726.

Conclusion: The shortening of LTT to only 2 measurements (baseline and 30-min) hardly leads to any differences in final results, and would entail savings in time, materials, and personnel.

Key words: Malabsorption syndromes. Lactose. Lactose tolerante test. Lactose intolerance.

INTRODUCTION

Lactose malabsorption (LM) is a very common condition; its frequency varies according to population ethnics, with a low prevalence in Northern European countries (< 5 %) as compared to Southern European (70-80 %) and Southeast Asian ones (approaching 100 %) (1,2).

Most common clinical symptoms include abdominal pain, diarrhea, bloating, flatulence, and vomiting following the ingestion of milk or milk-containing products (3). However, this sugar's malabsorption does not always translate into lactose intolerance (LI); in fact, only between one third and half of patients with LM are also lactose intolerants (1).

Different approaches are available for the diagnosis of LM, from lactase activity measurement in jejunal biopsy to absorption tests (lactose overload), through malabsorption studies (lactose hydrogen breath test, LHBT) and fecal analysis (fecal pH) (4). A novel method was recently developed for the diagnosis of lactose malabsorption –the gaxilose test– with promising results (5,6).

A lactose tolerance test (LTT) is a basic test of widespread use in county hospitals, high-resolution hospitals, and health centers because of its low cost and lack of complex infrastructure requirements. It consists of blood glucose measurements at different times following the ingestion of 50 g of lactose (baseline, 30, 60, 120 minutes). Drawbacks include potential symptoms (pain, diarrhea, flatulence, vomiting), its relatively invasive nature (multiple blood draws), and a prolonged duration (120 minutes) (7).

In the last few years industrial countries have pointed out a long-standing issue, namely the progressively increasing limitation of resources allotted for health care. Knowing which options –among all those available– will be more efficient (will yield better clinical results with lower associated costs) is important, and will result in greater therapy benefits with a lower cost (8).

Studies have been recently published showing that measurements at 120 min contribute nothing to LTT results, hence testing may be shortened to 60 min (9,10). We have seen that LTT may be further shortened with no significant changes in its results. This would entail reduced costs and time. The main goal of our study was to assess the feasibility and benefits of a simplified LTT shortened to 30 min, as well as its associated financial impact.

MATERIAL AND METHODS

Subjects

A multicenter, observational, cross-sectional study in a series of consecutive patients –from November 2011 to September 2012– with ≤ 16 years of age who underwent an oral lactose overload test for clinically suspected lactose intolerance (abdominal symptoms after exposure to dairy products or, when such association is unknown, presence of dysmotility, diarrhea or vomiting). Patients from the Andalusian Agencia Sanitaria Alto Guadalquivir (ASAG) hospitals in Andújar, Montilla, Sierra de Segura, Alcaudete, Alcalá la Real, and Puente Genil were included. *Agencia Sanitaria* covers a population of 253,000 inhabitants. Exclusion criteria included a history of celiac disease, hyperthyroidism/hypothyroidism, active inflammatory bowel disease, recent antibiotic/probiotic therapy (< 30 days), recent use of proton pump inhibitors/prokinetic agents (< 7 days), major abdominal surgery, drinking < 60 g alcohol a day, and diabetes mellitus (DM). Patients were withdrawn from the study if newly diagnosed with any of these conditions during the study.

All patients gave their consent before any exams were performed.

Design

Patients received a predefined lactose-free diet (LFD) for 7 days. Then they underwent LTT after being administered 50 g/250 mL lactose (Lactonaranja®, Bioanalitica SL, Spain) under fasting conditions, with blood draws from a vein at baseline, 30, and 60 min to measure blood glucose levels (mg/dL) using a Cobas® 8000 analyzer (Roche Diagnostics, Mannheim, Germany). LTT 60 was defined as testing for all three time points, and LTT 30 was defined as testing with no measurements at 60 min. The test was deemed abnormal (malabsorption) when glucose levels increased ≤ 20 mg/mL from baseline at any time point, this being the most widely accepted cut-off. Reproducibility was not affected by test shortening as the measurement protocol remains unchanged.

Lab measurements also included CBC, immunoglobulin A, anti-transglutaminase IgA antibodies, and thyroid-stimulating hormone (TSH) in order to identify potential exclusion criteria.

Financial analysis

The direct costs of an additional blood draw were estimated including both perishable materials (needles, vacuum systems, chemistry tubes, cotton swabs, surgical tape) and staff (nurses and lab technicians). Indirect costs derived from patient's lost time or in connection with false positive or false negative results –which prompt unnecessary additional testing (false positives) or repeat testing for symptom persistence in the absence of preventive actions (false negatives)– were not included.

Statistical method

Sample size was obtained using the GRANMO 7.12 software (IMIM Hospital del Mar, Barcelona, Spain); endorsing an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 205 subjects are required to detect a difference equal to or greater than 0.1 units, assuming a proportion of 0.45 in the reference group. A rate of 5 % losses to follow-up was estimated. Differences between LTT 60 and LTT 30 were analyzed using McNemar's test for two paired proportions. Agreement degree between LTT 60 and LTT 30 was measured using the kappa index and related 95 % confidence intervals. Differences in blood glucose level between patients with abnormal and normal test results were established using Student's T-test for independent means. Statistical significance was set at $p < 0.05$. The statistical analysis was carried out with the SPSS 16.0® software (SPSS, Inc., USA).

RESULTS

A total of 277 patients were enrolled in the study, and seven of these were excluded because of their meeting exclusion criteria (5 with type 2 DM, 1 with hypothyroidism, and 1 with adult celiac disease). All patients were Caucasians with a mean age of 39 ± 16 years; 69.6 % were women.

In all, 151 patients (55.9 %) had an abnormal LTT. Study-prompting symptoms included abdominal pain (65.6 %), bloating (50.4 %), diarrhea (50.4 %), vomiting (10.4 %), and stomach rumble (21.5 %). No statistically significant differences in baseline glycemia were spotted

between patients with normal and abnormal LTT results, but such differences were seen (as expected) at different time points (Table I).

Test result interpretation was changed for 6 patients (2.22 %) (McNemar's test: p = 0.03) when the 60-min time point was deleted. Table II illustrates diagnostic differences between LTT 30 and LTT 60, with their related agreement degree.

Table III shows an estimation of direct costs for a single time point measurement (60 min) in ASAG sites. During 2011, a total of 2,267 LTTs were carried out in ASAG sites; deletion of the 60-min time point during LTT procedures would have yielded savings of € 7,726, approximately, in direct costs.

Table I. Comparison of mean blood glucose levels at different time points between subjects with normal and abnormal LTT results

	Normal LTT	Abnormal LTT	p
Baseline glycemia (mg/dL)	92.6 (90.8-94.3)	90.1 (88.8-91.5)	0.134
Glycemia at 30 min (mg/dL)	131.5 (128.1-134.9)	96.4 (94.2-98.6)	0.002
Glycemia at 60 min (mg/dL)	113.8 (108.5-119.1)	90.4 (88-92.8)	0.0001

LTT: Lactose tolerance test; glycemia (95 % confidence interval); p: Statistical significance.

Table II. Diagnostic differences between LTT 30 and LTT 60

Test	Positive LTT*	Negative LTT*	False positives (%)**
LTT 60	151	119	
LTT 30	151	113	6 (2.22 %)
Kappa index (95 % CI)	p***		
0.95 (0.92-0.99)	p < 0.001		

LTT 30: Test shortened by deleting measurements at 60 min; *Positive and negative LTT results as compared to reference LTT 60 results; **A false positive result is considered for a positive LTT 30 with a negative LTT 60; ***p: Statistical significance.

Table III. An estimation of direct costs attributable to the 60-min time point in a lactose tolerance test as performed at Agencia Sanitaria Alto Guadalquivir sites in 2011

Direct costs	Time	Cost per patient (€)
I. Staff		
Nurse1[1]	4 minutes	1.1228
Laboratory technician[1]	4 minutes	0.8116
Subtotal		1.9344
II. Materials and perishable goods		
Materials for a blood draw[2]		0.6641
Cotton[3]		0.0022
Surgical tape[4]		0.0091
One 9-mL gelose-containing test tube[5]		0.1914
One serum glucose measurement6[6]		0.6068
Subtotal		1.4736
Total cost		3.408
Total of patients undergoing lactose testing at Agencia Sanitaria Alto Guadalquivir sites	Year 2011	2,267
Savings upon deleting the 60-min time point in 2011		7,726

[1]These costs were estimated based on the gross salaries of nurses (€28,059) and lab technicians (€20,283), and their 1,666 working hours per year, using ASAG's 2011 Annual Report. [2]Vacutainer (Becton-Dickinson) system including holder and Vacutainer Safety-Lok™; [3]Cotton use was estimated at 0.5 grams per patient. [4]Surgical tape use was similarly estimated at 5 cm per patient. [5]9-mL, yellow-capped blood collection tube with gelose (Vacuette). [6]Cobas® 8000 (Roche Diagnostics, Mannheim, Germany).

DISCUSSION

Several methods exist for the diagnosis of lactose malabsorption (LM). The measurement of lactase activity in jejunal biopsies has been proposed as gold standard (11). However, this is a much too aggressive test for the study of a mild condition, with results that may be influenced by irregular lactase activity distribution along the small bowel mucosa (1). Lactose hydrogen breath test (LHBT) represents the most commonly used indirect method for the diagnosis of LM as it is a non-invasive, reliable, inexpensive option (12). Sensitivity is very good (77.5 % on average) and specificity is excellent (97.6 % on average) (13). However, in addition to requiring 240 minutes for completion, false negatives are possible given the inability of the intestinal flora to release H_2 following the ingestion of non-absorbable carbohydrates or recently administered antibiotics, as well as false positives because of bacterial overgrowth. Shortened LHBTs (only 180 min) have been validated for the screening of lactose malabsorption when high-dose lactose is used for overload (14). Of late, a genetic test is available based on the detection of DNA polymorphism *C/T-13910*, whose C/C variant presents a strong correlation with poor lactase activity; however, drawbacks include a high cost and the lack of clinical information provided by lactose exposure (15).

Although LHBT is the most widespread approach, and the one supported with the highest number of literature references, many hospitals and outpatient clinics lack the necessary equipment, hence they are still using LTT on an ongoing basis. This is a minimally invasive test requiring 120 minutes for completion, with a sensitivity of 75 % and a specificity of 96 % in the adult (17). False negative results occur in patients with diabetes, bacterial overgrowth, and delayed gastric emptying. Two studies were recently reported, which show how suppressing measurements at 120 min has no impact whatsoever on test results (9,10); it is for this reason that our sites opted to implement an LTT variant shortened to 60 min.

In our results we saw that excluding glycemia measurements at 60 minutes results in a proportion of identified cases that remains virtually unchanged as compared to the complete procedure (only 2.22 % of false positives), with very high agreement and consistency levels (kappa index). Such data are comparable to those from the study by van Rossum HH et al. (10) in a Dutch population, with a false positive rate of 3 %. Furthermore, in various studies in India, the diagnostic efficacy of LTT 30, as measured with capillary samples, is very high when genetic testing is used as the gold standard (S 96.6 %, Sp 88.6 %, PPV 96.6 %, NPV 94.8 %) (16-17), and higher when 50 g rather than 25 g of lactose are used (18).

Financial assessments in the health setting are aimed at comparing the impact of an intervention on the health status of affected individuals *versus* its repercussions on resource use. A clear economical benefit has been shown

to result from boiling down traditional LTT (120 min) to shortened LTT (60 min) (9). Deleting another time point in LTT hardly involves any changes in terms of patient health since clinical outcomes are similar to those obtained when using full-length LTT, and more sensitive, specific tests may also be run for doubtful diagnoses.

Among study limitations the fact that LTT 30 was not compared to the gold standard should be highlighted, as it implies that this technique could not be validated for the diagnosis of lactose malabsorption with an estimation of diagnostic effectiveness. Regarding our analysis of direct costs as related to the deletion of one glycemic time point, our estimations are highly simplified, and indirect costs were not calculated given their complexity. Therefore, other potentially intervening factors were overlooked, including those derived from additional unnecessary testing (false positives) or repeat testing for symptom persistence in the absence of preventive actions (false negatives), patient's lost time, etc.

Future, well-structured studies comparing LTT 30 with the gold standard (jejunal biopsy) or other highly sensitive, highly specific validated techniques (e.g., gaxilose test) are needed to validate its diagnostic efficacy for lactose malabsorption.

A shortened LTT obviously benefits patients with one less draw and reduced waiting time; it similarly benefits the health system by saving up on time, personnel, and materials. Also, while the goal of the present study was not to compare LTT 30 *versus* other diagnostic methods, the fact that the time required for test completion would be one eighth of the standard LHBT length (240 minutes) must be underscored. Moreover, in contrast to genetic testing and lactase activity in duodenal biopsies, LTT provides patients with lactose overloads, which may result in valuable clinical information. Therefore, based on the above data, LTT 30 has some economic advantages over LTT 60, and their diagnostic consistency is high.

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