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ORAL ADMINISTRATION OF EXOGENOUS LACTASE IN TABLETS FOR PATIENTS DIAGNOSED WITH LACTOSE INTOLERANCE DUE TO PRIMARY HYPOLACTASIA

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ABSTRACT - ***Background*** **-** Primary hypolactasia is a common condition where a reduced lactase activity in the intestinal mucosa is present. The presence of abdominal symptoms due to poor absorption of lactose, which are present in some cases, is a characteristic of lactose intolerance. ***Objective*** **-** Evaluate the efficacy of a product containing exogenous lactase in tablet form compared to a reference product with proven effectiveness in patients with lactose intolerance. ***Methods*** **-** Multicentre, randomized, parallel group, single-blind, comparative non-inferiority study. One hundred twenty-nine (129) adult lactose intolerance patients with hydrogen breath test results consistent with a diagnosis of hypolactasia were randomly assigned to receive the experimental product (Perlatte® - Eurofarma Laboratórios S.A.) or the reference product (Lactaid® - McNeilNutritionals, USA) orally (one tablet, three times per day) for 42 consecutive days. ***Results*** **-** Data from 128 patients who actually received the studied treatments were analysed (66 were treated with the experimental product and 62 with the reference product). The two groups presented with similar baseline clinical and demographic data. Mean exhaled hydrogen concentration tested at 90 minutes after the last treatment (Day 42) was significantly lower in the experimental product treated group (17±18 ppm versus 34±47 ppm) in the per protocol population. The difference between the means of the two groups was -17 ppm (95% confidence interval [95% CI]: -31.03; -3.17). The upper limit of the 95% CI did not exceed the *a priori* non-inferiority limit (7.5 ppm). Secondary efficacy analyses confirmed that the treatments were similar (per protocol and intention to treat population). The tolerability was excellent in both groups, and there were no reports of serious adverse events related to the study treatment. ***Conclusion*** **-** The experimental product was non-inferior to the reference product, indicating that it was an effective replacement therapy for endogenous lactase in lactose intolerance patients.

HEADINGS - Lactase. Lactose intolerance. beta-Galactosidase. Clinical trial.

INTRODUCTION

Lactose (β-galactosyl-1,4-glucose) is a disaccharide that is produced by the mammary gland in most mammals. When ingested, lactose is hydrolysed in the small intestine into two monosaccharides (glucose and galactose) that are absorbed via active transport[7]. The hydrolysis of this molecule is catalysed by the enzyme β-galactosidase or lactase, which is present in the brush border of the intestinal villi.

The presence of excessive lactose in the intestinal lumen due to lactase deficiency (hypolactasia) creates an osmotic gradient such that water and sodium are secreted into the lumen of the small intestine, thereby increasing the volume and decreasing the consistency of the intestinal contents and accelerating gastrointestinal transit[2]. Unabsorbed lactose reaches the colon, where it is fermented by bacteria. This digestion produces short chain fatty acids and gases (including carbon dioxide, methane and hydrogen) and may promote gastrointestinal symptoms. The presence of abdominal symptoms due to poor absorption of lactose observed in some patients clinically defines lactose intolerance (LI).

When present, LI is characterized by the presence of abdominal pain and distention, and bloating. The patient may also complain of flatulence, diarrhoea, and borborygmi, and less frequently nausea and vomiting[2]. Increased methane production can occasionally cause reduced intestinal transit and constipation. The intensity of these gastrointestinal symptoms varies considerably depending on the degree of lactase deficiency and the presence of other pathophysiological mechanisms related to functional gastrointestinal disorders.

A non-invasive and reliable diagnostic method for lactose malabsorption is the hydrogen breath test, which involves the oral administration of up to 50 g of lactose, followed by measurements of the concentration of exhaled hydrogen over a period of 3 to 6 hours after administration[2,13].

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The exhaled hydrogen levels are increased in lactase deficiency cases, corroborating an LI diagnosis. LI was defined in a recent National Institutes of Health (NIH) conference as the onset of gastrointestinal symptoms following a blinded, single-dose challenge of ingested lactose by an individual with lactose malabsorption, which are not observed after ingestion of an indistinguishable placebo. However, this procedure is not used in clinical practice[11].

LI treatment seeks to control the symptoms and involves food re-education, with restrictions on the consumption of milk and its derivatives, the consumption of pre-digested dairy products, and/or enzyme replacement therapy via the ingestion of exogenous lactase[10]. The safety of exogenous lactase products has been confirmed in countries where they are approved and widely commercialized as food supplements.

In Brazil, the first functional food (oral tablet) containing lactase was recently studied and received marketing approval by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária – ANVISA). This study was conducted as part of its clinical development programme to evaluate the efficacy and safety of this product compared to a product whose efficacy as an endogenous lactase replacement therapy was previously demonstrated in LI patients[1,3-5,8,12,14].

METHODS

Patients from both genders, between 18 and 60 years of age, with a history consistent with LI confirmed by the hydrogen breath test were included in this multicentre, randomized, parallel group, single-blind, non-inferiority comparative study. The exclusion criteria were as follows: history of smoking, presence of secondary hypolactasia, colonoscopy or enema performed in the four weeks prior to inclusion in the study, presence of comorbidities that might interfere with participation in the study, or a history of allergy to lactase or any other component of the study treatments formulations. The study was approved by the Research Ethics Committees of the centres, and all patients signed an informed consent form prior to inclusion in the study.

Eligible patients were randomly allocated in a 1:1 ratio by centralized randomization and stratified by centre to receive the experimental product (EP) (Perlatte® - Eurofarma Laboratórios S.A.) or the reference product (Lactaid® - McNeilNutritionals, USA). Both products were administered orally using a 9,000 FCC dose tablet (1 FCC unit is defined as the amount of enzyme that releases o-nitrophenol at a rate of 1 mol/min under the conditions established by the *Food Chemicals Codex*) before major meals (breakfast, lunch, and dinner) for 42 consecutive days. Although it was not possible to mask the shapes of the pills, the products were provided in identical packages, and only one member of the team at each study site was responsible for the study treatment dispensation and accountability, whereas all other members of the study team (including the investigator) remained blind to the treatment received.

Eligible subjects were evaluated in four in-person visits to the study centres at the following time points: Day 0 (randomization visit), Day 14, Day 28 and Day 42 (final visit). During the randomization visit (Day 0), the subjects were randomly assigned to one of the two treatment groups. During subsequent visits, the hydrogen breath test (measured as the concentration of hydrogen exhaled at 0, 30, 60, 90, 120, 150 and 180 minutes after the ingestion of 25 g of lactose) was conducted starting 30 minutes after administration of the study treatment, which was administered at the study centre. During the test, specific gastrointestinal symptoms (diarrhoea, pain, abdominal distension and flatulence) were scored. Data on tolerability and the occurrence of adverse events (AEs) were collected during each study visit.

The primary efficacy endpoint was defined as the exhaled hydrogen concentration 90 minutes after the ingestion of 25 g of lactose measured on Day 42 (final visit) in the per protocol (PP) population. Secondary endpoints included the exhaled hydrogen concentration over 180 minutes on Day 42 in the PP and intention to treat (ITT) populations, the exhaled hydrogen concentration over the period of time of the study (data not shown) and the scores for specific symptoms (diarrhoea, pain, abdominal distension, and flatulence) recorded during the hydrogen breath test and evaluated through a visual analogue scale (VAS, 0 [absent] to 10 [most intense possible]). Safety endpoints included the overall evaluation of treatment tolerability by the patient and the investigator (VAS, 0 [absent] to 10 [excellent]) at each visit as well as the occurrence of AEs.

Sample size calculation and statistical analysis

To demonstrate the non-inferiority of the EP compared to the RP, a value representing the largest difference between both study treatments in the mean exhaled hydrogen concentration that did not indicate clinical inferiority was chosen. Thus, 48 cases in each treatment group would be necessary to detect a difference of mean exhaled hydrogen concentration of 7.5 ppm by Student's *t*-test with a power of 80% and a significance level of 5%. Increasing the power of the test to 90%, while maintaining the other assumptions, resulted in a sample size of 64 patients per study arm. Assuming a dropout rate of approximately 10%, the total estimated sample size was 140 patients (70 patients per treatment group).

Normally distributed continuous variables were summarized by the mean and standard deviation (SD), and non-normal continuous variables were summarized by the median and interquartile range (IQR, 25th to 75th percentiles). Normality was verified using Kolmogorov-Smirnov test. Categorical variables were described by their relative frequencies. Two-tailed 5% significance levels were used to designate significant differences between groups when appropriate.

The primary efficacy analysis was performed by comparing the mean exhaled hydrogen at 90 minutes at the final study visit (Day 42) between both study groups in the PP; this population included the subjects who did not violate the eligibility criteria or the protocol and had their exhaled hydrogen concentration measured at 90 minutes during the baseline period. The 95% confidence interval (95% CI) for the mean difference between the concentrations obtained for the EP and RP groups was calculated. To demonstrate non-inferiority, the upper limit of the 95% CI for the difference between groups needed to be less than or equal to 7.5 ppm.

Secondary efficacy analyses were performed for PP and ITT populations, which included all subjects that met the eligibility criteria and had at least one measurement of any of the study endpoints. The resulting data were compared between the two treatment groups using Student's t test or Mann-Whitney test for normally and non-normally distributed data, respectively. The safety population used for the EA frequency analysis in both study groups consisted of all subjects who received at least one dose of the study treatment and had at least one safety evaluation.

Missing data were not imputed. Statistical softwares R (version 2.13.1) and MedCalc (version 11.3.3.0) as well as Excel (2007, Microsoft Office) were used in the analyses.

RESULTS

Between September 2011 and January 2012, 129 patients were randomly assigned to the study groups. Figure 1 shows the flow of the participants in the study by treatment group, indicating the composition of PP and ITT populations.

The two study groups showed similar baseline clinical and demographic data (Table 1). Adherence to the study treatment was also similar in both treatment groups.

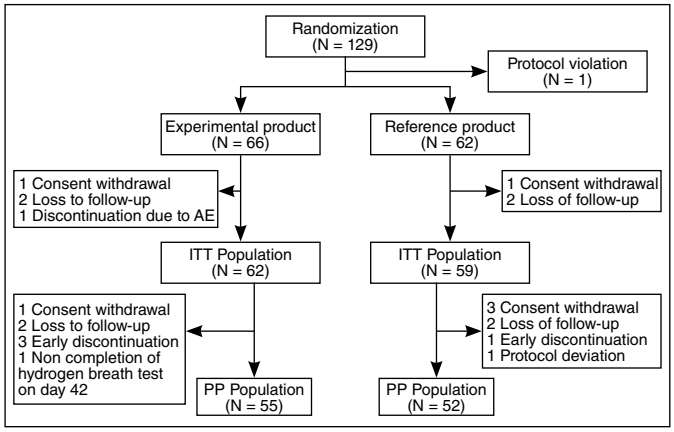

FIGURE 1. Flow of subjects in the study

Primary efficacy analysis

The mean exhaled hydrogen concentration after 90 minutes during the final visit (Day 42) was significantly lower in the EP treated group compared to the RP group (17 ± 18 ppm versus 34 ± 47 ppm, respectively) for the PP. The difference between the means of both groups (EP – RP) was -17ppm, with a 95% CI = [-31.03; -3.17]. To demonstrate the non-inferiority of the EP compared to the RP, the upper limit of the 95% CI for the difference should not exceed 7,5 ppm (*a priori* non-inferiority limit). Once the observed limit was -3.17ppm, the non-inferiority of the EP compared to the RP was confirmed. A larger data dispersion was observed in the RP group, especially for values above the median (Figure 2).

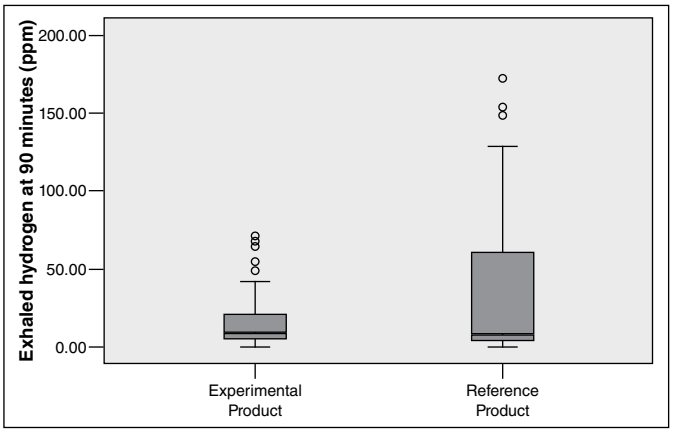

FIGURE 2. Exhaled hydrogen concentration at 90 minutes on Day 42 (per protocol population)

Secondary efficacy and safety analyses

Table 2 shows the exhaled hydrogen concentrations over the 180-minute test time frame on Day 42 for both PP and ITT populations. A generalized linear model analysis for repeated measures did not show a significant difference between the groups (P=0.058 and P=0.066 for PP and ITT populations, respectively) but showed a significant

TABLE 1. Demographic data by treatment group (PP and ITT populations).

	PP Population			ITT Population		
	Experimental Product	Reference Product	*P*	Experimental Product	Reference Product	*P*
Age, years						
Mean ± SD	40.6 ± 11.4	40.6 ± 11.1	0.960*	40.5± 11.4	40.6± 11.1	0.931*
Min - Max	18.7 - 60.8	19.3 - 59.7		18.7 - 60.8	19.3 - 59.7	
Gender, N (%)						
Female	57 (85.1)	51 (76.1)	0.275[&]	58 (84.1)	51 (76.1)	0.286[&]
Male	10 (14.9)	16 (23.9)		11 (15.9)	16 (23.9)	
Race, N (%)						
Caucasian	60 (89.6)	65 (97.0)	0.165[&, a]	62 (89.9)	65 (97.0)	0.165 [&, a]
Black	2 (3.0)	0 (0)		2 (2.9)	0	
Asian	2 (3.0)	1 (1.5)		2 (2.9)	1 (1.5)	
Mixed race	3 (4.5)	1 (1.5)		3 (4.3)	1 (1.5)	
BMI, kg/m^2						
Median (IQR)	24.2 (21.7; 26.0)	24.0 (21.4; 27.1)	0.620**	24.2 (21.7; 26.1)	24.0 (21.4; 27.1)	0.621**

BMI: body mass index; IQR: interquartile range; ITT: intention to treat; Max: maximum value; Min: minimum value; PP: per protocol; SD: standard deviation; (*) Student's *t*-test, (**) Mann-Whitney test; (&) Fisher's exact test; (a) *P*-value for comparisons between Caucasian versus Others (Black, Asian and Mixed race).

TABLE 2. Exhaled hydrogen concentration over the 180 minutes of the test performed during the final study visit (Day 42) in both treatment groups (PP and ITT populations).

Hydrogen concentration (ppm)	Time						
	0 min	30 min	60 min	90 min	120 min	150 min	180 min
PP Population							
Experimental product (N=55)							
Median (IQR)	5 (3 - 11)	6 (4 - 14)	7 (4 - 15)	9 (5 - 22)	10 (4 - 33)	13 (4 - 32)	14 (3 - 41)
Min - Max	0 - 83	0 - 84	1 - 81	0 - 71	1 - 160	0 - 149	1 - 172
Reference product (N=52)							
Median (IQR)	4 (1 - 9)	5 (2 - 10)	8 (4 - 28)	8 (3 - 63)	12 (4 - 58)	17 (5 - 76)	22 (5 - 71)
Min - Max	0 - 39	0 - 83	1 - 166	0 - 172	0 - 188	0 - 166	0 - 174
ITT Population							
Experimental product (N=62)							
Median (IQR)	5 (3 -11)	6 (4 -14)	7 (4 - 15)	9 (5 - 22)	10 (4 - 33)	13 (4 - 32)	14 (3 - 41)
Min - Max	0 - 83	0 - 84	0 - 81	0 - 71	1 - 160)	0 - 149	1 - 172
Reference product (N=59)							
Median (IQR)	4 (1 - 9)	5 (2 - 10)	8 (4 - 28)	8 (4 - 60)	12 (4 - 58)	18 (5 - 75)	23 (5 - 68)
Min - Max	0 - 39	0 - 83	1 - 166	0 - 172	0 - 188	0 - 166	0 - 174

IQR: interquartile range. ITT: intention to treat; Max: maximum value; Min: minimum value; PP: per protocol.

time effect (P<0.0001 for both populations), meaning that the hydrogen concentration in the exhaled air increased in both groups as time went through. A significant interaction effect was observed between time and group (P=0.011 and P=0.012, respectively), indicating that there were differences in the efficacy over the 180 minutes when the two treatments were compared. Beginning at 60 minutes, the difference between the hydrogen concentrations in both groups increased, with the EP being more effective. The results obtained from for the PP population are graphically shown in Figure 3.

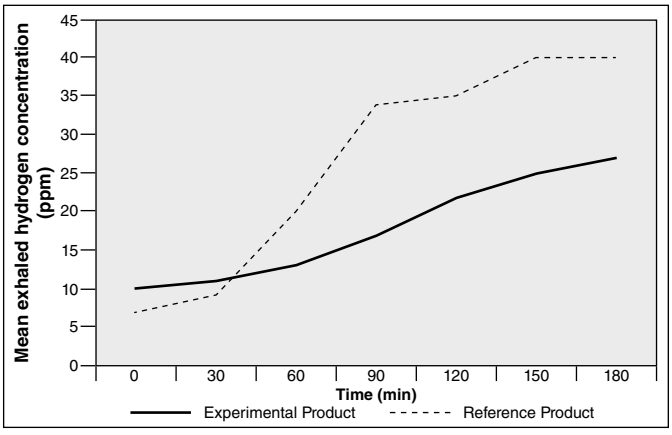

FIGURE 3. Exhaled hydrogen concentration over the 180 minutes of the test performed on the final visit of the study (Day 42) in both treatment groups (per protocol population)

Once a single subject could have reported more than one of the four types of abdominal symptoms recorded during the 180 minutes of the hydrogen breath test conducted at each visit, we chose to analyse the VAS score of the most intense episode of each symptom reported during each exam. In other words, the mean/median value (for normally/non-normally distributed data, respectively) of the most intense occurrence of each discomfort (highest VAS) was compared between groups. Table 3 shows the results obtained on days 28 and 42 in the PP population. With the exception of the significantly higher average score for flatulence in the group receiving the RP on Day 28 (P=0.041), there were no significant differences between the groups in the intensity of symptoms during

TABLE 3. Comparison between groups of the most intense discomfort reported during the hydrogen breath test (PP population).

Symptom (VAS - cm)	Experimental product (N=55)	Reference product (N=52)	*P*
Day 28			
Diarrhoea	N=5	N=3	&
Mean ± SD	5.2 ± 3.1	6.3 ± 3.5	
Min - Max	2.0 - 10.0	3.0 - 10.0	
Flatulence	N=12	N=17	0.041*
Mean ± SD	3.1 ± 2.2	5.0 ± 2.5	
Min - Max	0.0 - 8.0	2.0 - 10.0	
Pain	N=7	N=6	0.642*
Mean ± SD	5.6 ± 3.2	4.8 ± 2.1	
Min - Max	0.0 - 9.0	1.0 - 7.0	
Distension	N=8	N=7	0.336**
Median (IQR)	1.5 (1.0 - 7.5)	3.0 (3.0 - 6.0)	
Min - Max	0.0 - 9.0	2.0 - 8.0	
Day 42			
Diarrhoea	N=1	N=5	&
Median (IQR)	2.0	7.0 (4.5 - 7.5)	
Min - Max	2.0 - 2.0	4.0 - 8.0	
Flatulence	N=14	N=12	0.106**
Median (IQR)	2.0 (1.8 - 4.0)	4.5 (2.0 - 6.8)	
Min - Max	0.0 - 10.0	1.0 - 8.0	
Pain	N=2	N=1	&
Mean ± SD	7.5 ± 2.1	8.0	
Min - Max	6.0 - 9.0	8.0 - 8.0	
Distension	N=5	N=5	0.746*
Mean ± SD	3.8 ± 3.4	5.2 ± 2.9	
Min - Max	1.0 - 8.0	2.0 - 8.0	

PP: per protocol; Max: maximum value; Min: minimum value; N: number of patients with the discomfort; SD: standard deviation; (&): the sample size did not allow this parameter to be calculated; (*) Student's *t*-test; (**) Mann-Whitney test.

the hydrogen test performed during the various study visits. Similar results were seen in the ITT population.

Figure 4 shows graphically the results for the treatment tolerability according to the patients at the last study visit (PP). The vast majority of the subjects gave a score of 10 (excellent tolerability), with no significant difference between the two treatment groups (P=0.417; Mann-Whitney test). The results were similar for the ITT population and for analysis from the other study visits (PP and ITT populations).

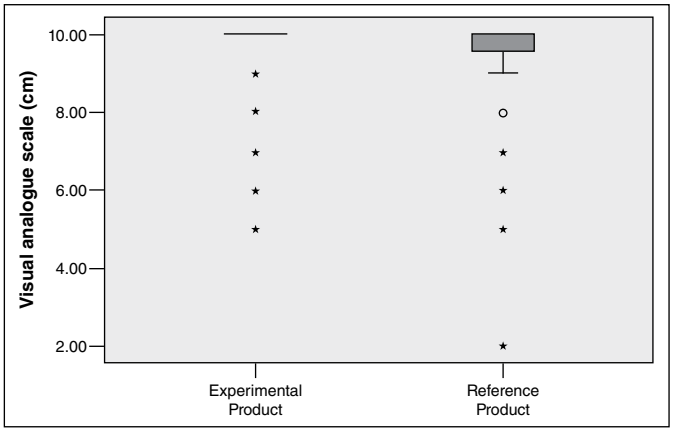

FIGURE 4. Boxplot of the overall tolerability to the treatment reported by the subjects on Day 42 (per protocol population)

Similarly, the investigators scored tolerability as a 10 (excellent tolerability) for the vast majority of the subjects in the PP population, especially those treated with the EP (Figure 5). No significant difference was observed between both treatment groups (P=0.193; Mann-Whitney test). Similar results were observed for the ITT population and for the analyses of data from other visits (PP and ITT populations).

Forty-one (41) subjects treated with the EP experienced at least one of the 313 AEs reported in this group, whereas 38 subjects experienced at least one of the 322 AEs reported in the RP group. Table 4 shows the AEs reported by >3% of the population regardless the presence of causal relationship with the study treatment, for which the relative difference between the number of patients in each group that experienced the AE at least once was analysed. Hypothesis tests were performed for the 13 AEs with a relative difference ≥10% between the groups, and no significant differences were found in their frequencies.

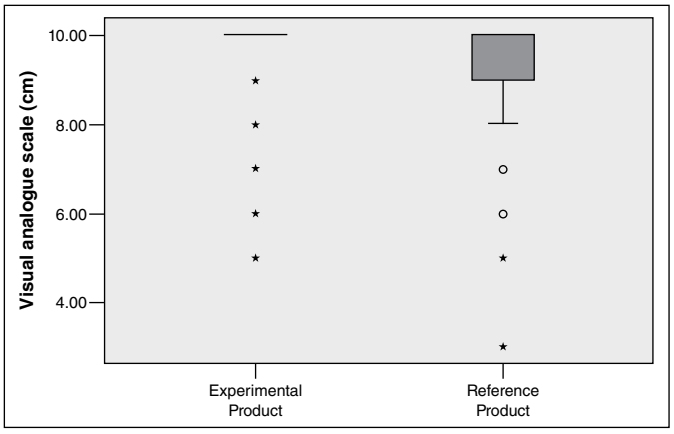

FIGURE 5. Boxplot of the overall tolerability score for the treatment on Day 42 as reported by the investigator (per protocol population)

Twenty-one (21) of the most frequent AEs were considered by the investigators as possibly or probably related to the study treatment, of which 12 were reported by the EP-treated group and 9 were by the RP-treated group. No AE was considered definitely related to the treatment. Only one serious adverse event (acute appendicitis) was reported during the study, which was considered by the investigator as not related to the study treatment. This subject was discontinued prematurely from the study.

TABLE 4. Most common adverse events in the safety population and the relative differences between treatment groups

Adverse event	Frequency in the safety population (%)	Experimental product (N=64)	Reference product (N=60)	*P**
Flatulence	38.7	21	27	0.198
Abdominal pain	34.7	20	23	0.453
Diarrhoea	32.3	20	20	-
Nausea	13.7	11	6	0.301
Headache	16.1	9	11	0.627
Abdominal distension	16.1	8	12	0.330
Upper abdominal pain	9.7	8	4	0.366
Myalgia	5.6	5	2	0.441
Dizziness	4.0	4	1	0.366
Malaise	4.0	3	2	1.000
Epigastric burning	6.4	3	5	0.720
Vomiting	3.2	3	1	0.620
Itching	3.2	2	2	-
Gastroesophageal reflux	3.2	1	3	0.353
Bloating	3.2	1	3	0.353

* Fisher's exact test.

DISCUSSION

Primary hypolactasia is an extremely common condition whose prevalence varies widely between ethnicities, with extremely low rates in North European countries and particularly high rates in South America, Africa, Asia and Australia[2,6]. There is no accurate data on its prevalence in our country (Brazil). Gastrointestinal symptoms, such as abdominal distension and pain, flatulence, nausea and diarrhoea, are present in approximately one-third of cases, clinically indicating the presence of LI[2].

Treatment of LI involves improvement of the presenting symptoms. Restricted consumption of milk and its derivatives and the use of commercially available or homemade pre-digested dairy products in liquid or paste form through the addition of exogenous lactase are used in our country. However, these methods limit dietary options. The variety of available pre-digested products decreases their practicability due to the need to prepare the milk, which involves time consuming procedures, and is only possible in food provided in a liquid or paste form. Products with exogenous lactase in tablet form to be taken before eating dairy foods were developed to improve the practicability and reduce the restrictions on dietary options. Administration of exogenous lactase as pills has been used to treat LI in children, adolescents and adults, and enzymatic supplementation was recently shown to be an intermediate step between dairy restriction and the use of diets with low levels of fermentable oligo-, di- and monosaccharides and polyols (FODMAPS)[8,9,12].

This study analysed the efficacy of the first functional food approved in our country containing exogenous lactase. The study was designed as a non-inferiority study where the efficacy of the new product was compared to a reference product whose efficacy was demonstrated against a placebo. The non inclusion of a placebo-treated group is justified by the existence of a proven therapy to reduce exhaled hydrogen in the breath tests of LI patients. The primary outcome used (concentration of hydrogen in the exhaled air) is widely used in studies involving LI.

The primary efficacy analysis showed the non-inferiority of the EP compared to the RP, demonstrating its efficacy. Although the study was not designed as a superiority study, the, analysis of the primary endpoint suggests the superiority of the EP over the RP once the mean concentration of exhaled hydrogen was significantly lower in the EP-treated group 42 days after the beginning the study treatment. The reduced dispersion of the results observed in the experimental group at the end of the studied treatment indicated that the results were consistent and showed increased homogeneity in the results associated with EP administration. The secondary efficacy analyses showed similar results, corroborating the similarity between the products.

The tolerability of both treatments was excellent. The vast majority of reported AEs were considered unrelated to the study treatments, and correspond to frequent presenting symptoms of LI patients.

CONCLUSION

The experimental product containing exogenous lactase in orally administered tablets was non-inferior to the reference product, demonstrating its potential effectiveness for the treatment of LI. The treatment was safe, and tolerability was excellent.

Authors' contributions

Francesconi CFM: recruitment for the study, data collection, interpretation of results and manuscript writing. Machado MB: recruitment for the study and data collection. Steinwurz F: recruitment for the study and data collection. Nones RB: recruitment for the study and data collection. Quilici FA: recruitment for the study, data collection and manuscript revision. Catapani WR: recruitment for the study, data collection and manuscript revision. Miszputen SJ: recruitment for the study, data collection and manuscript revision. Bafutto M: recruitment for the study, data collection and manuscript revision.

Francesconi CFM, Machado MB, Steinwurz F, Nones RB, Quilici FA, Catapani WR, Miszputen SJ, Bafutto M. Administração oral de lactase exógena em comprimidos em pacientes portadores de intolerância à lactose devido à hipolactasia primária. Arq Gastroenterol. 2016,53(4):228-34.

RESUMO - ***Contexto*** - A hipolactasia primária é uma condição muito frequente na qual há redução da atividade da lactase na mucosa intestinal. A presença de sintomas abdominais devidos à má absorção da lactose presente em alguns casos caracteriza a intolerância à lactose. ***Objetivo*** - Avaliar a eficácia de um produto contendo lactase exógena em comprimidos comparativamente a de um produto comparador com eficácia comprovada em pacientes portadores de intolerância à lactose. ***Métodos*** - Estudo multicêntrico, randomizado, de grupos paralelos, com investigador cego, comparativo de não-inferioridade. Cento e vinte e nove (129) pacientes adultos portadores de intolerância à lactose e teste do hidrogênio no ar expirado compatível com o diagnóstico de hipolactasia foram randomizados para receber o produto experimental (Perlatte® - Eurofarma Laboratórios S.A.) ou o produto comparador (Lactaid® - McNeil Nutritionals, EUA), por via oral (um comprimido, três vezes ao dia), durante 42 dias consecutivos. ***Resultados*** - Os dados dos 128 pacientes que efetivamente receberam o tratamento do estudo foram avaliados (66 tratados com o produto experimental e 62 com o produto comparador). Os dois grupos se mostraram homogêneos quanto aos dados demográficos e clínicos basais. A média da concentração do hidrogênio expirado aos 90 minutos no teste realizado ao final do tratamento (Dia 42) foi significativamente menor no grupo tratado com o produto experimental (17±18 ppm versus 34±47 ppm na população por protocolo). A diferença entre as médias dos dois grupos foi de -17 ppm (intervalo de confiança de 95% [IC95%]: -31,03; -3,17). O limite superior do IC95% não ultrapassou a margem de não-inferioridade estipulada *a priori* (7,5 ppm). As análises secundárias de eficácia confirmaram a semelhança entre os tratamentos (populações por protocolo e com intenção de tratamento). A tolerabilidade foi excelente em ambos os grupos e não houve relato de eventos adversos graves relacionados ao produto. ***Conclusão*** - O produto experimental se mostrou não-inferior ao produto comparador, indicando sua eficácia no tratamento substitutivo da lactase endógena em pacientes portadores de intolerância à lactose.

DESCRITORES - Lactase. Intolerância à lactose. beta-Galactosidase. Ensaio clínico.

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