PRESENCE OF LACTOSE IN MEDICATIONS FOR THE TREATMENT OF HYPERTENSION

PRESENÇA DE LACTOSE EM MEDICAMENTOS PARA O TRATAMENTO DA HIPERTENSÃO

PRESENCIA DE LACTOSA EN MEDICAMENTOS PARA EL TRATAMIENTO DE LA HYPERTENSION

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ABSTRACT

Introduction: Medications used to treat hypertension in the Brazilian population, containing lactose as an excipient in solid pharmaceutical form, cause undesirable effects in patients with lactose intolerance.

Objective: To ascertain the presence of lactose as an excipient in medications in solid pharmaceutical form available on the market that are used to treat hypertensive patients.

Methodology: To evaluate the medications present in the National List of Essential Medicines (Rename), indicated for the treatment of hypertension or comorbidities that may occur alongside hypertension. Generic, similar, and reference medications were selected from the market to evaluate the drug information and determine the presence or absence of lactose.

Results: Of the 151 medications analyzed and grouped according to pharmaceutical forms, therapeutic classes, brands, and categories, data regarding the presence of lactose were collected from the electronic drug information database of the National Health Surveillance Agency (ANVISA) and from pharmaceutical industry websites. It was detected that lactose is

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present in 60.93% of the selected medications, being more frequent in tablets (60.87%) and coated tablets (39.13%), and no lactose was found in dragees, respectively. It was predominantly found in reference medications (47.83%), followed by generics (31.52%), and similar medications presented a proportion of 20.65%.

Conclusion: Lactose is one of the most used excipients in solid medications, as it provides greater resistance to the form. 60.93% of the analyzed medications contain lactose in their formulation; therefore, it is essential to include a warning phrase on medication boxes due to the risk posed to people with lactose intolerance.

Keywords: Hypertension. Intolerance. Lactose. RENAME.

RESUMO

Introdução: Medicamentos utilizados no tratamento de hipertensos na população brasileira, tendo a lactose como excipiente em forma farmacêutica sólida, ocasionando efeitos indesejáveis nos pacientes com intolerância à lactose.

Objetivo: Constatar a presença de lactose como excipiente em medicamentos na forma farmacêuticas sólidas disponíveis no mercado que são utilizados no tratamento de pacientes hipertensos.

Metodologia: Avaliar os medicamentos presentes na Rename, indicados para o tratamento de hipertensão ou comorbidade que possam vir junto a hipertensão. Foram selecionados medicamentos genéricos, similares e referências no mercado para avaliar o bulário e constatar ou não a presença da lactose.

Resultados: Dos 151 medicamentos analisados e agrupados de acordo com as formas farmacêuticas, classes terapêuticas, marcas e categorias, dados quanto a presença de lactose no bulário eletrônico da Agência Nacional de Vigilância Sanitária (ANVISA) e nos sites da indústria farmacêutica. Detectou-se que a lactose está presente em 60,93% dos medicamentos selecionados, sendo mais frequentes nos comprimidos (60,87%) e comprimidos revestidos (39,13%) e nas drágeas não foi encontrado a presença de lactose, respectivamente. Ela foi constatada, predominante, em medicamentos referência (47,83%), seguida de genéricos (31,52%) e os medicamentos similares apresentaram a proporção de 20,65%.

Conclusão: A lactose é um dos excipientes mais utilizados nos medicamentos sólidos, por proporcionar uma maior resistência a forma. 60,93% dos medicamentos analistas a lactose está presente em sua formulação, portanto, é fundamental frase de alerta nas caixas dos medicamentos, devido ao risco causado a pessoas com intolerância.

Palavras-chave: Hipertensão. Intolerância. Lactose. RENAME.

RESUMEN

Introducción: Los medicamentos utilizados en el tratamiento de pacientes hipertensos en la población brasileña contienen con frecuencia lactosa como excipiente en formas farmacéuticas sólidas, ocasionando efectos indeseables en pacientes con intolerancia a la lactosa.

Objetivo: Verificar la presencia de lactosa como excipiente en medicamentos en formas farmacéuticas sólidas disponibles en el mercado que se utilizan en el tratamiento de pacientes con Hypertension.

Metodología: Evaluar los medicamentos incluidos en la RENAME, indicados para el tratamiento de la hipertensión o comorbilidades asociadas; se seleccionaron medicamentos genéricos, similares y de referencia disponibles en el mercado para analizar los prospectos y constatar la presencia o ausencia de lactosa.

Resultados: De los 151 medicamentos analizados y agrupados según formas farmacéuticas, clases terapéuticas, marcas y categorías, los datos sobre la presencia de lactosa se obtuvieron de los prospectos electrónicos de la Agência Nacional de Vigilância Sanitária (ANVISA) y de los sitios web de la industria farmacéutica; se detectó que la lactosa está presente en el 60,93% de los medicamentos seleccionados, siendo más frecuente en comprimidos (60,87%) y comprimidos recubiertos (39,13%), mientras que no se encontró en grageas; se constató predominantemente en medicamentos de referencia (47,83%), seguido de genéricos (31,52%) y los similares representaron el 20,65%.

Conclusión: La lactosa es uno de los excipientes más utilizados en medicamentos sólidos por proporcionar mayor resistencia estructural; el 60,93% de los medicamentos analizados contienen lactosa en su formulación, por lo tanto, es fundamental incluir advertencias en los envases debido al riesgo para personas con intolerancia.

Palabras clave: Hipertensión. Intolerancia. Lactosa. RENAME.

1 INTRODUCTION

Dosage forms is the final state that the active ingredients present after being submitted to pharmaceutical operations, in order to facilitate administration and obtain the greatest desired therapeutic effect, with precise dosage and excellent stability. They are presented in a more practical way to be administered, as agglomerated solids, including tablets, tablets, capsules, tablets, pills and granules, with tablets being the most considerable form in the pharmaceutical industry. (BARRIENTOS, et al. 2018).

Aiming at maximum excellence in drug production, known inactive ingredients of excipients are combined and added to give adequate stability to their dosage form. Lactose is a type of sugar most used in manufacturing since the 60s as a solid excipient, as it has excellent physicochemical stability, mild flavor, availability, high crushing resistance, low cost and benefits, the disadvantages of using lactose as an excipient and that a percentage of the population is intolerant to it (BARRIENTOS, et al. 2018).

Hypolactasia, also known as lactose intolerance, is a syndrome of varying gastrointestinal symptoms following consumption of lactose-containing foods, resulting in a minimal ability to digest lactose and glucose at the brush border of the mucosa of the small intestine. When lactose is not digested, it is fermented by the intestinal microbiota, causing symptoms of lactose intolerance such as: flatulence, pain, bloating, diarrhea, borborygmus, even vomiting (COSTANZO, et al 2019).

The Brazilian legislation, RDC 47 of September 8, 2009, points to the qualitative description of the excipients in the package insert of medicines and the attachment of expressions aiming to take all the necessary measures for the use of medicines. The alert guidelines regarding active ingredients and excipients in package inserts and drug labeling are regulated by RDC 60, of December 17, 2010, but the presence of excipients in package inserts and labeling do not have a detailed legislation on which excipients were used in the preparation, aiming only at the rational use of drugs. Lactose has been one of the most used excipients, as it favors the absorption of calcium in the body, in addition to its multifunctionality. However, it is not discriminated in the boxes, making it implicit to the consumer, and may lead to reactions according to the degree of sensitivity of the individual who has lactose intolerance (NOVAES, 2020).

Lactose can be found as an adjuvant in several medications, such as drugs that are used in the treatment and control of Systemic Arterial Hypertension (SAH), also known as high blood pressure, remains one of the main determinants of morbidity and mortality in the country and in the world. The predominance of hypertension in the Brazilian population is around 38 million people, according to the national health survey, becoming increasingly

precocious, representing a serious Public Health problem in Brazil and in the world (MELO, et al. 2020).

Although there is an increase in global SAH rates, this increase does not occur in a similar way between economies. Middle- and low-income countries have shown more significant growth (31.5%) than high-income countries (28.5%). The increase in the number of people with SAH reflects different aspects of the population's living condition (MELO, et al. 2020).

Population aging, added to unhealthy lifestyles, with the preference for processed, fatty, saltier foods, alcohol consumption, smoking, people with diabetes, dyslipidemia and lack of physical activity, have contributed to this increase. Other aspects such as the knowledge, control and treatment of SAH are also highly sensitive to individual and socioeconomic attributes (MELO, et al. 2020). Aiming at the treatment of chronic diseases such as hypertension and the reduction of morbidity and mortality, non-drug measures or those associated with antihypertensive drugs are used, including coptopril, simvastatin and enalapril maleate, drugs that have lactose as an excipient in their formulation (MOURA, et al. 2015)

The reason for the present study was to verify the presence of lactose as an excipient in drugs in the solid pharmaceutical form available on the market that are used in the treatment of hypertensive patients.

2 METHODOLOGY

This is a descriptive study, with a quantitative approach, carried out in April and June 2022. The therapeutic class used in the study followed the guidance of the National List of Medicines (RENAME) by anatomical chemical therapeutic classification (ATC) for drugs of the cardiovascular system (BRASIL, 2022). From the therapeutic classes described for the cardiovascular system, drugs definitively for hypertension were selected, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and drugs associated with the care of patients with hypertension as lipid-modifying agents.

A total of 151 drugs from 32 brands were selected, grouped according to pharmaceutical forms, therapeutic classes and categories. The pharmaceutical forms analyzed were: tablets, coated tablets and tablets.

The excipients indicated in the professional brochures available in the electronic leaflet of the National Health Surveillance Agency (ANVISA) and on the websites of the pharmaceutical industry were carefully analyzed.

3 RESULTS

Of the 151 drugs selected for the study, 92 (60.93%) contained lactose in the excipients. Table 1 shows the distribution of the drugs, according to the pharmaceutical form. Among all the drugs that contained lactose, the tablets were the most frequent (60.87%), followed by the coated tablets (39.13%) and the presence of lactose was not found in the pills.

Table 1

Presence of lactose according to the pharmaceutical form of the drugs used in the treatment of hypertension. Brazil, June 2022

Pharmaceutical form	n	Presence of lactose n (%)	Proportion* (%)
Tablet	81	56 (69,14)	60,87
Coated tablet	68	36 (52,94)	39,13
Dragea	2	0 (0,00)	0,00
TOTAL	151	92 (60,93)	100,00

* Proportion calculated in relation to the total number of drugs used in the treatment of hypertension with lactose (n = 92).
Source: The authors.

In the therapeutic classes according to ATC analyzed (Table 2), it was found that almost all drugs in these classes contained lactose in their excipients. Lipid-modifying agents (38.04%) and agents acting on the renin-angiotensin system (23.91%) had the highest proportion of lactose in their excipients. Beta-blockers and diuretics contributed with a frequency of more than 10% and hypertensive and calcium-blockers contributed with a frequency of less than 10%.

Considering the categories of drugs analyzed, the highest occurrence of lactose was found in reference drugs (47.83%), followed by generics (31.52%) and similar drugs presented a proportion of 20.65%.

Table 2

Presence of lactose according to the therapeutic class according to PCI of the drugs used in the treatment of hypertension. Brazil, June 2022

Therapeutic class	n	Presence of lactose n (%)	Proportion* (%)
Lipid-modifying agents	41	35 (85,37)	38,04
Agents acting on the Renin-Angiotensin System	25	22 (88,00)	23,91
Antihypertensive	20	7 (35,00)	7,61
Beta-blockers	37	15 (40,54)	16,30
Calcium channel blockers	11	2 (18,18)	2,17
Diuretics	17	11 (64,71)	11,96

TOTAL	151	92 (60,93)	100,00

* Proportion calculated in relation to the total number of drugs used in the treatment of hypertension with lactose (n = 92).
Source: The authors.

The classes of drugs used in the treatment of hypertension were related to the categories of reference, generic and similar drugs. The presence and absence of lactose are presented in Table 3. In this relationship, considering the total number of drugs evaluated, lactose was found more frequently in the reference lipid-modifying agents and the agents that act on the reference renin-angiotensin system.

Table 3

Presence of lactose according to the category of drugs used in the treatment of hypertension. Brazil, June 2022

Classification of medicinal products	n	Presence of lactose n(%)	Proportion * (%)
References	67	44 (65,67)	47,83
Generic	49	29 (59,18)	31,52
Similar	35	19 (54,29)	20,65
TOTAL	151	92 (60,93)	100,00

* Proportion calculated in relation to the total number of drugs used in the treatment of hypertension with lactose (n = 92).

Source: The authors.

Table 4

Distribution of the drug classes used in the treatment of hypertension, according to the presence or absence of lactose. Brazil, June 2022

Class/Category	References		Generic		Similar	
	Yes	No	Yes	No	Yes	No
Lipid-modifying agents	19	2	12	3	4	1
Agents acting on the Renin-Angiotensin System	9	3	8	0	5	0
Antihypertensive	4	6	1	4	2	3
Beta-blockers	6	7	5	8	4	7
Calcium channel blockers	0	5	0	2	2	2
Diuretics	6	0	3	3	2	3

Source: The authors.

The classes of drugs used in the treatment of hypertension were related to the categories of reference, generic and similar drugs. The frequencies of presence and absence of lactose are presented in Table 4. In this relationship, considering the total number of drugs used in the treatment of hypertension evaluated, lactose was found in higher frequency in reference (12.58%) and generic (7.94%) lipid-modifying agents, followed by drugs that act

on the reference Renin-Angiotensin System (5.96%) and generics (5.29%). Antihypertensive drugs, beta-blockers, and calcium channel blockers had a higher frequency of lactose-free drugs when compared to the same class with lactose. In the class of diuretic drugs in the reference drug category, 100% of this category had lactose in the formulation.

4 DISCUSSION

The present study showed that more than half of the evaluated drugs used in the treatment of hypertension contain lactose in their formulation. This substance is present, in greater proportion, in the form of tablets and coated tablets, respectively. Because of the characteristics, the main studies related to the functionality of lactose in solids have been reported in studies in the development of tablet formulations (GOHEL; JOGANI, 2005). The present study reported that the presence of lactose among the tablets and coated tablets was 60.93% in the medications evaluated for hypertension. Lactose is widely used in the development of the tablet and coated tablet dosage forms because they provide the formulations with appropriate conditions to prevent possible alterations such as adhesion to punctures and lack of uniformity of the tablet's appearance (STEFANI et al, 2009).

Lactose can be found in medications administered orally and could bother patients with lactose intolerance. However, it is likely that the amount of this sugar is too small to cause symptoms related to intolerance (PHILPOTT et al, 2014). Commercially, lactose is produced from cow milk whey and is widely used for the purpose of diluting and filling in capsules and tablets (LUYT et al., 2014). Symptoms of lactose intolerance arise from malabsorption resulting from little or no lactase enzyme activity. There is considerable variation considering the characteristics of each person in the severity of gastrointestinal symptoms according to the amount of lactose ingested and also the digestion capacity of each individual (DI RIENZO et al., 2013).

The dose of lactose in most pharmaceutical products usually does not exceed 2 g/day. Therefore, it is unlikely that more severe symptoms can be attributed to lactose in a solid drug administered orally, especially in adults who have not been previously diagnosed with severe lactose intolerance (LUYT et al., 2014).

Studies carried out by Montalto et al. (2008) evaluated the influence of lactose in patients with lactose intolerance. In this study, we evaluated the excretion of H2 in the exhaling air and symptoms of lactose intolerance in patients with lactose intolerance after ingestion of a capsule containing 400 mg of lactose or placebo through the randomized, crossover, double-blind, controlled study. 77 patients with lactose intolerance were evaluated in the H2 breath tests with 400 mg lactose and 400 mg placebo. Gastrointestinal symptoms

occurring within 8 hours of ingestion of the different substrates were assessed by a visual-analogue scale. With this study, it was possible to verify that the ingestion of 400 mg of lactose did not cause a significant difference in the results.

In the study conducted by Areias, Sousa and Paulino (2014), the presence of lactose and parabens in oral drug formulations used by elderly patients with vestibular diseases was evaluated. In this study, it was found that of the medications used by this group, 80% of the elderly in the study used medications containing lactose and 61% of them were exposed to lactose concomitantly using 2 or more medications containing this excipient, which could be considered a greater risk for the elderly who were more sensitive or intolerant to lactose. The most cited antihypertensive drugs in this study were captopril and enalapril and the diuretic hydrochlorothiazide. It is important to emphasize that all these drugs are commonly used in the treatment of the elderly, especially those affected by vestibular diseases and their comorbidities.

However, a case study evaluated a 72-year-old male patient with a history of lactose intolerance, who was supported by acute myocardial infarction. The patient was discharged with dual antiplatelet therapy (acetylsalicylic acid and clopidogrel), rosuvastatin, perindopril and carvedilol. However, he was re-admitted in the following days due to abdominal pain, flatulence, diarrhea and nausea, despite not ingesting lactose-containing food products. To solve the problem, a new prescription was made with lactose-free formulations of fluvastatin, metoprolol, lisinopril and isosorbide mononitrate. He was also advised to use clopidogrel in conjunction with probiotics and lactase supplementation, since he is allergic to aspirin and all clopidogrel and triflusal m formulations contain lactose. Shortly thereafter, the patient was completely asymptomatic in both gastrointestinal and cardiovascular terms (BARRA, MARQUES, 2012).

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