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Association between the Use of Proton Pump Inhibitors and Cognitive Impairment in Older Adults

Asociación entre uso de inhibidores de la bomba de protones deterioro cognitivo en adultos mayores

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ABSTRACT

Objective: The objective was to describe the association between the presence of cognitive impairment and the use of proton pump inhibitors (PPI) in the older adult population in Bogotá, Colombia. **Methods:** We analyzed the SABE Bogotá study. This study included 2,000 people over 60 years, in a cross-sectional sample. The variable of interest was the alteration in the modified Mini-Mental State Examination (MMSE-M). It was related to the use of PPI. This analysis was adjusted for factors such as sex, age, years of schooling and marital status. **Results:** The average age was 71.17±8.05 years, 63.4% were women. We found that 20.7% used PPIs, with an average duration of use of 74.8±93.76 months. 12.6% of older adults had altered MMSE-M, with a higher prevalence in PPI users (25.4% vs. 20.02%; p: 0.049). In the multivariate analysis, an association of adjusted risk increase was found between cognitive impairment and the use of PPIs for ≥24 months (OR: 1.90; CI: 1.11-3.24; p = 0.018). **Conclusions:** This study shows an association of a significant increase in the risk between using PPIs for ≥ 24 months and developing cognitive impairment. More studies are needed to conclude a direct causality relationship.

Keywords
older adults; cognitive impairment; proton pump inhibitors.

RESUMEN

Objetivo: Describir la asociación entre la presencia de alteración cognoscitiva y el uso de inhibidores de la bomba de protones (IBP) en la población adulta mayor de Bogotá, Colombia. **Métodos:** Se analizaron los datos del estudio SABE-Bogotá, que incluyó 2.000 personas mayores de 60 años de edad, en una muestra transversal probabilística por conglomerados. La variable de interés fue la alteración en el Mini-Mental

State Examination Modificado (MMSE-M), la cual se relacionó con el uso de IBP, ajustado por factores como sexo, edad, escolaridad y estado civil. **Resultados:** La edad promedio fue de 71,17±8,05 años, y el 63,4% eran mujeres. El consumo de IBP se encontró en el 20,7% de la población estudiada, con un tiempo de uso promedio en meses de 74,8±93,76. El 12,6% tenía el MMSE-M alterado, siendo mayor la prevalencia en los consumidores de IBP (25,4% vs. 20,02%; p= 0,049). En el análisis multivariado se encontró una asociación de aumento de riesgo ajustado entre el deterioro cognitivo y el uso de IBP por ≥ 24 meses (OR: 1,90; IC: 1,11-3,24; p = 0,018). **Conclusiones:** Este estudio muestra una asociación de aumento de riesgo significativa entre deterioro cognitivo y el consumo de IBP durante ≥ 24 meses. Se necesitan más estudios que permitan concluir una relación directa de causalidad.

Palabras clave
anciano; disfunción cognitiva; inhibidores de la bomba de protones.

Introduction

The world is experiencing a demographic transition with a noticeable increase in the population aged 60 years or older. This phenomenon, which is particularly rapid in Latin American countries, is a great medical and social achievement. However, this brings social, cultural, economic and health challenges, given the high prevalence of chronic diseases, among which dementia and cognitive impairment are specially important (1).

The worldwide prevalence of dementia is estimated to be 35.6 million, and it is expected to rise to 150 million in 2050 (2). It is the third leading cause of death in Europe, accounting for 8.57% of the total number of deaths (2). Neurocognitive disorders can significantly affect the quality of life of elderly people and their families (3).

Therefore, it is important to detect interventions that make it possible to develop effective strategies to prevent and control risk factors for the onset of cognitive impairment (4), such as the appropriate use of medications (5). It has recently been suggested that the use of proton pump inhibitors (PPI) could favor the development of cognitive impairment (6). These drugs have shown a clear benefit in the pathologies for which they are indicated; but they are often prescribed inappropriately (7,8).

Some have suggested that this association is due to an alteration in vitamin B12 absorption, secondary to atrophy of the gastric mucosa, which in turn is produced by hypochlorhydria, acidification of the lysosomes of the microglia. In addition, it has been found that there may be an alteration in beta- and gamma-secretases, enzymes known to be involved in Alzheimer's disease (9,10).

Limited data are available in Latin America on this subject. Therefore, the primary objective of this study is to describe the link between cognitive impairment and the use of PPIs in the older adult population of Bogotá, Colombia.

Material and methods

We analyzed data from the SABE (Spanish acronym for Health, Well-Being and Aging) study. This cross-sectional study was conducted in 2012 in Bogotá, and included 2,000 people aged 60 years or older (81.9% of the eligible people who finally agreed to participate in the study). We used a probabilistic sampling by conglomerates which is statistically representative of the city's population of 779,539 subjects aged 60 years or older. This instrument was derived from the international tool SABE, previously applied in other studies, modified and adapted to the Colombian context (11,12,13).

The SABE Bogotá study included 11 main topics, ranging from sociodemographic aspects, living conditions, poverty and violence, to health status, including cognitive status, anthropometric measurements, functional assessment, disabilities and access to health services.

The teams of interviewers were trained by the lead investigators, thematic researchers, statistician and field coordinator. The results were collected on paper, and then two programmers in Excel for Windows transferred them to a separate database.

All the people signed an informed consent in order to participate in the study. This study was approved by the Ethics Committee of

the Pontificia Universidad Javeriana, Bogotá, Colombia.

Variables

Dependent variable

The dependent variable of interest was alteration in the cognitive tests, determined according to the score obtained in the Modified Mini Mental State Examination (MMSE-M), an instrument validated in Spanish and widely used in this study; this questionnaire has a minimum score of 0 and a maximum of 19. The cutoff point is 13 (0-12 "deterioration" and 13-19 "without deterioration") (14). It includes: Orientation (4 points), Registration of 3 words (3 points), Attention and Calculation (5 points), Comprehension (3 points), Recall (3 points), Drawing (1 point), with a sensitivity of 93,.8 and a specificity of 93.9 (15).

Independent variables

Older adults who scored more than or equal to 13 in the MMSE-M were asked verbally about PPI use and duration of use (months); otherwise, this information was requested from the proxi. To minimize memory bias, they were asked to show the box or the packaging of the medication they were using at the time. The PPIs were omeprazole, lanzoprazole, pantoprazole and esomeprazole.

In addition, sociodemographic variables were included for adjustment, such as age, sex, marital status (dichotomized in married and single), and years of schooling; comorbidities were also included, such as diabetes, chronic obstructive pulmonary disease, hypertension, cardiovascular disease, cerebrovascular accident, arthropathies and depression.

Statistical analysis

Univariate analysis was used to explore the extreme values and the normal distribution to adjust and categorize variables. The categorical variables are expressed as frequencies and percentages, while for the continuous variables the means and standard deviations were used. The association between the dependent variable and the independent variables was analyzed; chi-square tests were used for categorical variables and T-tests for continuous variables. Based on the ROC curve, better sensitivity and specificity figures were found, time of PPI use greater than or equal to 24 months was selected, and it was dichotomized again. We performed a multivariate logistic regression model, in which the outcome variable was cognitive impairment, and the independent variable was unadjusted PPI use, and then adjusted for sex, age, marital status and years of schooling, to obtain odds ratio (OR) with 95% confidence intervals. A variable of interaction was used between the age and the time of use of the drug, given that said variable (age) is affecting both the outcome and the independent variable of interest. The level of statistical significance was established at $p < 0.05$. The data was analyzed with Stata Version 14 for iOS.

Results

A total of 2,000 older adults were evaluated. The average age was 71.17 ± 8.05 years, 63.4% were women, 35.75% were married, the average number of years of schooling was 5.52 ± 4.58. The prevalence of PPI use was 20.7%, with an average duration of use of 74.8 ± 93.76 months. The MMSE-M was altered in 12.6% of the older adults (Table 1).

Table 1
Description of the sample and bivariate analysis

Variable	Cognitive impairment Median ± SD or n (%)	Without cognitive impairment Median ± SD or n (%)	P value	Total Median ± SD or n (%)
PPI use	64 (25.4)	350(20.02)	0.049	414 (20.7)
Duration of PPI use	59.5 ± 67	77.6 ± 97.6	0.155	74.8 ± 93.76
Age	79.2 ± 8.23	70.02 ± 7.3	< 0.001	71.8 ± 8.05
Women	172 (68.25)	1096 (62.7)	0.0087	1268 (63.4)
Married	65 (25.7)	650 (37.2)	< 0.001	715 (35.75)
Schooling	2.3 ± 2.95	5.98 ± 4.58	< 0.001	5.52 ± 4.58

SD: standard deviation.

In the bivariate analysis, statistically significant associations were documented among older people with cognitive impairment and older age, female sex, being unmarried, a low schooling level and use of PPIs, all with p less than 0.05 (Table 1).

In the multivariate analysis, PPI use for 24 or more months, adjusting for the variables of age, sex, level of schooling and marital status, showed a 1.90 times increase in the risk of association (OR: 1.90; CI: 1.11-3.24; p = 0.018) (Table 2).

Table 2
Multivariate analysis

	Not adjusted (OR; 95% CI; p value)	Adjusted (OR; 95% CI; p value)
PPI use	1.35; 1.01-1.84; 0.05	1.14; 0.80-1.63; 0.450
PPI use > 24 months	1.55; 1.11-2.17; 0.01	1.90; 1.11-3.24; 0.018

Adjusted for age, sex, marital status, schooling and comorbidities CI: confidence interval.

Discussion

This study shows a significant association of increased risk between using PPIs for 24 or more months and developing cognitive impairment.

There is a high prevalence of cognitive impairments in Latin America (16,17). Therefore, it is very important that health systems focus on their prevention, with the control of risk factors as a pillar (18,19).

Studies have found the biological feasibility of the association between PPI use and cognitive impairment in murine models. This may have implications for human beings, as has been observed in developed countries where research has been conducted on PPIs and their positive association with cognitive impairment, as shown in this study in the Latin American context, where information on the subject is limited (6,9).

Initial evidence shows a significant increase in the occurrence of cognitive impairment in PPI users (6,20). However, in contrast to previous research, a recent longitudinal study conducted in the United States found no association between the use of PPI and cognitive impairment. This is probably due to methodological differences between the studies (21).

There are divergent and not entirely conclusive concepts on this hypothesis; in addition, there is a high degree of heterogeneity among these studies, due to the differences in their methodological designs.

This study has some limitations. First, as it was a cross-sectional study, it was not possible to determine the causality of the associations. Second, the dependent variable is self-reported, which can lead to memory bias, and because of the cross-sectional characteristics of the survey it was not possible to establish the previous MMS-E score, as well as the non-discrimination of the cognitive impairment severity, which was assessed by a scale and not by a specialized medical examination. On the other hand, this study has important strengths. It is noteworthy that it shows an association of a hypothesis with limited information in the subject area; another strength is that this is the first epidemiological study in older people in Bogotá that measures the association between PPI use and cognitive impairment.

This study demonstrated a positive association between cognitive impairment and PPI use. This leads to the formulation of new longitudinal studies to obtain more scientific information to establish causality and thus create public health policies to reduce the incidence of neurodegenerative disorders.

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