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The Association Between Cognition and Histamine-2 Receptor Antagonists in African Americans

Malaz Boustani, MD, MPH[*,†,‡], **Kathleen S. Hall, PhD**[§], **Kathleen A. Lane, MS**[¶], **Hisham Aljadhey, PharmD**[‖], **Sujuan Gao, PhD**[¶,**], **Frederick Unverzagt, PhD**[§], **Michael D. Murray, PharmD, MPH**[†,‖], **Adesola Ogunniyi, MD**[††], and **Hugh Hendrie, MB, ChB, DSc (Med)**[*,†,§]

[*]Indiana University Center for Aging Research, Indianapolis, Indiana

[†]Regenstrief Institute Inc., Indianapolis, Indiana

[‡]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina

[§]Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina

[¶]Department of Medicine, University of North Carolina, Chapel Hill, North Carolina

[‖]Division of Pharmaceutical Outcomes and Policy, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina

[**]Division of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana

[††]Department of Medicine, University College Hospital, Ibadan, Nigeria

Abstract

Objectives—To evaluate the association between histamine-2 receptor antagonist (H2A) exposure and incident cognitive impairment in a community-based sample of African Americans.

Design—Five-year longitudinal observational study.

Participants—A sample of 1,558 community-dwelling African Americans aged 65 and older with no baseline cognitive impairment living in Indianapolis, Indiana.

Outcome Measure—Incident cognitive impairment, defined as incident dementia, cognitive impairment without dementia, or poor cognitive performance, as determined using combined cognitive assessments that included the Community Screening Instrument for Dementia, a comprehensive clinical assessment including informant interview, and neuropsychological testing.

Exposure—Trained interviewers assessed the use of prescription and over-the-counter H2As using in-home inspection of medications and report of participants and informants.

Results—Incident cognitive impairment occurred in 275 (17.7%) participants. After controlling for age, education, baseline cognitive score, the use of anticholinergics, and history of diabetes mellitus and depression, continuous use of H2As was associated with greater risk of incident cognitive impairment than for nonusers (odds ratio = 2.42; 95% confidence interval = 1.17–5.04).

Conclusion—H2As might be a risk factor for the development of cognitive impairment in African Americans. This finding requires confirmation from future studies.

Address correspondence to Malaz Boustani, MD, MPH, Regenstrief Institute, Inc., 1050 Wishard Blvd., RG6, Indianapolis, IN 46202. mboustani@regenstrief.org.

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Keywords

cognitive impairment; risk factor; histamine antagonists

Adramatic rise in the prevalence of cognitive impairment, comorbid chronic disease, and exposure to multiple medications has accompanied the aging of the U.S. population.[1,2] There were an estimated 7 million cases of dementia in the United States in 2000, and this number may grow to 18.5 million by 2050.[3] On average, older Americans suffer from two to three chronic diseases such as hypertension, diabetes mellitus, osteoarthritis, and coronary artery disease.[2,4] This comorbidity has led to a higher rate of medication use in older adults attending primary care clinics; the average number of medications is five to six.[2] A significant number of these medications, such as antihistamines, have anticholinergic activities with negative cognitive effects.[2]

Proton pump inhibitor (PPI) and histamine-2 receptor antagonists (H2As), including cimetidine, ranitidine, famotidine, and nizatidine, are among the most widely used pharmacological therapy for various gastrointestinal disorders in older adults.[5] Using pharmacy billing data, it is estimated that, over a 1-year period, 1.3% of U.S. patients took at least one H2A and 1.6% took at least one PPI for more than 3 months.[6] Excluding over-the-counter use, ranitidine and famotidine are among the top medications prescribed in the United States, with more than 16 million prescriptions dispensed in 2005.[7]

Over the past decade, research on the effect of H2A use on the cognitive function of older adults has produced inconsistent findings.[8–14] In earlier observational studies, protective effects were reported with the use of these agents for incident Alzheimer's disease (AD).[9,11] This possible beneficial effect was evaluated in a pilot randomized trial, but the results were negative.[14] Data from this trial indicated that H2As had potentially negative effects on the cognitive function of older adults.[14] Other cross-sectional and longitudinal data analyses have also suggested adverse cognitive effects with the use of H2As.[10,13] The sources of the inconsistencies between studies might be due primarily to methodological biases such as the measurement of the outcome or the exposure and the adjustment for potential confounders.

This article benefits from the prospective 5-year follow-up and clinically validated measurement of incident cognitive impairment of the Indianapolis–Ibadan Dementia Project to explore the association between the use of H2As and incident cognitive impairment in a cohort of elderly African Americans that are underrepresented in research studies.

Methods

The Indiana University–Purdue University at Indianapolis institutional review board approved the study, and all participants provided informed consent.

Study Population and Design

The Indianapolis Water Company constructed a random sample of 60% of residential addresses within 29 contiguous U.S. Census tracts in Indianapolis. Interviewers went door to door to sampled addresses and invited African Americans aged 65 and older to participate. This sample was representative of African Americans aged 65 and older throughout Indianapolis in age, sex, and socioeconomic composition. When possible, a close relative within the subject's household was also interviewed regarding the primary participant's daily functioning.

Of the 7,590 residential addresses provided by the public utility, 4,915 households were ineligible, because none of the members of the household were aged 65 and older, and 383 households had no African-American family members (282 households had two interviews, and four households had three interviews). Of the 2,582 eligible participants, 249 refused participation, and 121 were too ill to participate; 2,212 participants were enrolled.

The study included three waves of data collection: a baseline prevalence study followed by incidence studies 2 and 5 years after baseline.[15–18] The study followed a two-stage design in which the Community Screening Interview for Dementia (CSI-D)[19] was administered to all study participants in the first stage, and a full clinical assessment was carried out in a subsample of subjects in the second stage. Using the scores on the CSI-D for sampling into the clinical assessment stage, study participants were placed in one of three performance groups: poor performance (100% invited for clinical assessment), intermediate performance (50% sampled), and good performance (5% sampled). If individuals who were sampled from the good or intermediate group refused or were unable to participate, replacements were sampled. This sampling method was weighted so that the individuals with the highest probability of having dementia would be selected, as well as including a small sample of good performers to test for false negatives.

Cognitive and Clinical Assessment

The CSI-D assesses cognition and has a section for interviewing a relative about daily functioning. The cognitive scale assesses short- and long-term memory, abstract thinking, judgment, and higher cortical function (aphasia, agnosia, apraxia, and constructional ability). An interview with a close relative provided data on the subject's activities of daily living and social function. The scores from the cognitive scale and the interview with the relative were combined into a single screening outcome measurement of a discriminant function score that demonstrated 87.0% sensitivity and 83.1% specificity in distinguishing persons with dementia from those without[18] with an area of 98% under the receiver operating characteristic curve.[19] When informants were available, the study used discriminant scores for grouping individuals into good-, intermediate-, and poor-performance groups. When informants were unavailable, cognitive scores alone were used to determine performance group. The classification into performance group also included decline in CSI-D score from previous waves.

The Stage 2 clinical assessment was conducted during a home visit and included the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD),[20,21] a standardized physical and neurological examination and functional status review,[22] a semi-structured interview with a relative, and a request for medical records. Dementia was diagnosed according to *International Classification of Diseases, 10th Revision*,[23] and the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*,[24,25] criteria. Cognitive impairment with no dementia was diagnosed if there was an informant report of a clinically significant decline in cognitive function or evidence of significant cognitive decline on physician examination or impaired CERAD test performance and no or only minimal impairment in activities of daily living.

End Point

Onset of incident cognitive impairment was defined as the first time a participant was in the poor performance group according to screening, was classified as having dementia, or suffered from cognitive impairment without dementia according to clinical diagnosis as defined in the previous section at follow-up Waves 1 or 2. Participants in the good or intermediate group at all participating waves were considered to be cognitively unimpaired.

Medication Interview

Information on medication use was collected at each wave. Trained interviewers asked participants and informants to retrieve from the rooms of the home all prescription and nonprescription medications that the participant was taking at the time of the interview. Interviewers recorded the names of medications from the labels of each container. Only the names of drugs were recorded from the labels; there was no attempt to record dosage, frequency, or duration of drug use. When drug containers were unavailable, the interviewer recorded the drug name as reported by the participant or informant or from active drug lists kept by participants. It was estimated that 82% of the medication-related data came from direct inspection of the drug container.

Continuous use of a drug was defined as participant or informant indicating that the participant used the drug at all participating waves. Intermittent use of drug was defined as the participant or informant indicating that the participant used the drug at at least one, but not all, participating waves. A trained pharmacist reviewed the medication lists (including generic and trade names) collected by the study interviewers and created various drug classes, including the class H2A (cimetidine, famotidine, nizatidine, and ranitidine) and the class PPI (omeprazole and lansoprazole). In addition, a new variable was constructed that included any medication with definite central anti-cholinergic activities.[2]

Analysis

T tests and one-way analysis of variance (ANOVA) were used for continuous variables and Fisher exact tests for categorical variables when comparing the demographic characteristics of participants with and without cognitive impairment and between the three medication usage groups. Age was the participant's age at the end point. The association between outcome (incident cognitive impairment) and exposure (H2A and PPI use) was analyzed using logistic regression models that included potential confounders. These confounders were selected if they were univariately statistically associated with incident cognitive impairment or H2A usage at the $\alpha = 0.15$ level. The final logistic regression model included covariates that were significant at the $\alpha = 0.05$ level in addition to history of depression or diabetes mellitus and any use of medications with definite central anticholinergic activities. These variables were included because of their potential association with incident cognitive impairment. Odds ratios (ORs), 95% confidence intervals (CIs), and *P*-values were calculated from the final model.

Results

Of the 2,212 participants who completed the baseline in-home interviews, 312 were excluded from this analysis because of dementia diagnosis (n = 65), cognitive impairment no dementia (n = 106), or poor performers (n = 141). Thus, the at-risk population included 1,900 potential subjects who had no cognitive impairment at baseline. This study was restricted to the 1,558 subjects who completed the 2-year follow-up or the 2- and 5-year follow-up waves and had all of the relevant data collected at each participating wave (20 had missing baseline characteristics, 133 had died before Wave 1 assessment, 58 refused at Wave 1, and 131 could not be located or other reasons).

The end point of incident cognitive impairment occurred in 275 of the study participants (105 participants in Wave 1 and 170 in Wave 2). A comparison of the demographic, medical history, and baseline medication usage of participants with and without incident cognitive impairment is provided in Table 1. As expected, the impaired participants were older (80.6 ± 7.2 vs 77.0 ± 6.2, $P < .001$), had fewer years of education (9.1 ± 3.2 vs 10.1 ± 2.9, $P < .001$), and had lower baseline CSI-D cognitive scores (30.5 ± 1.9 vs 31.3 ± 1.5, $P < .001$).

Of the 1,558 study participants, 203 were using at least one H2A during one of the three data collection time points (38 individuals were continuous users, 165 were intermittent users, 70 were cimetidine users, 11 were famotidine users, 62 were nazitidine users, and 75 were ranitidine users), and 1,355 never used any H2As. As summarized in Table 2, women and persons with diabetes mellitus or depression were more likely to use these drugs.

In addition, 17.0% of the H2A never-users, 19.4% of the intermittent users, and 34.2% of the continuous users had incident cognitive impairment ($P = .03$). After adjusting for potential confounders such as education, age, baseline CSI-D score, the use of drugs with definite central anticholinergic activities, history of diabetes, and history of depression, our data demonstrated that the continuous use of H2A was significantly associated with greater risk of incident cognitive impairment than for nonusers (OR = 2.42, 95% CI = 1.17–5.04, $P = .02$, Wald chi-square (χ^2) = 5.63); intermittent use of H2A was not associated with such a risk (OR = 1.17, 95% CI = 0.76–1.81, $P = .47$, Wald $\chi^2 = 0.52$).

PPIs have been used as an alternative to H2As in the treatment of gastrointestinal disorders in older adults. Thus, their association with incident cognitive impairment and therefore their role as an alternative therapy was evaluated. There were 44 subjects using at least one PPI during one of the waves, including one individual using a PPI at all participating waves. There was no association between PPI use and incident cognitive impairment (OR = 0.80, 95% CI = 0.33–1.90, $P = .61$, Wald $\chi^2 = 0.27$) after adjusting for the potential confounders used in the H2A analysis.

Discussion

Using 5 years of longitudinal observational data and after adjusting for potential confounders (age, education, baseline cognition, any use of drug with definite central anti-cholinergic activities, history of depression, history of diabetes mellitus), this study showed that the continuous use of H2As by African Americans aged 65 and older who were cognitively intact at baseline was associated with greater risk of developing incident cognitive impairment (OR = 2.42, 95% CI = 1.17–5.04) than for H2A nonusers.

These findings are in agreement with recent longitudinal observational analyses of 2,082 community-dwelling older adults in North Carolina.[13] The North Carolina study used cognitive decline as the outcome, determined as differences in the Short Portable Mental Status Questionnaire (SPMSQ) score measured over 7 years. In this study, the use of H2As was a risk factor for subsequent cognitive decline (risk ratio = 1.51, 95% CI = 0.93–2.47). These findings are also consistent with the results from the single clinical trial evaluating the efficacy of H2As (150-mg daily dose of nazitidine) in delaying the progression of cognitive decline in older adults with AD.[14] Although this trial showed no positive effects of nazitidine on any of the clinical cognitive outcome measures over the 1-year study interval, there were some trends toward deleterious effects for nazitidine on patients' memory and language.[14]

Nevertheless, the findings of the current study are not consistent with the results from other longitudinal and cross-sectional studies.[9,11,12] In 1995, one study compared H2A exposure in pairs of siblings with and without AD.[9] Siblings who used H2As for a sustained time experienced a later onset of AD than those were not exposed to any.[9] Analyses of the cross-sectional data from the Cache County Study indicated similar protective effects.[11] However, neither longitudinal data from the same Cache county study nor cross-sectional data from the Rotterdam Study showed an association between H2A usage and incident AD.[10,12]

The reasons for the inconsistencies in results between studies are not readily apparent. Populations included in these studies were different (cognitively normal subjects vs subjects

at high risk for dementia, African Americans vs other populations). The study design used (cross-sectional, prospective cohort, case–control) and the outcome criteria varied between studies (defining cognitive impairment based on a screening vs comprehensive neuropsychological assessment, using incident AD vs cognitive decline). The current study included cognitively normal subjects, had a prospective design, and used incident cognitive impairment defined according to a comprehensive neuropsychological assessment. The possible different effects for the various drugs of the H2A class may also explain these inconsistent findings, although the current study had a limited number of subjects to explore these various effects. Furthermore, there were differences in the method used to determine exposure to H2As (home-based review of the medication vs survey questionnaire) and the control for potential confounders in the analysis.

The mechanism responsible for the adverse cognitive effects associated with H2As is not clear. Suggested mechanisms include vitamin B_{12} deficiency associated with H2A use and the potential anticholinergic effect of some H2As. Certain H2As, such as ranitidine and cimetidine, have anti-cholinergic activities that lead to the development of delirium and other cognitive deficits.[26–29] H2As use could result in vitamin B_{12} deficiency that leads to cognitive deficit. Stomach acidity is necessary for the removal of vitamin B_{12} from dietary protein sources before it can be absorbed, so it might be that H2A prevents the absorption of vitamin B_{12}.[30] Because the body contains enough vitamin B_{12} stores for 2 to 5 years, a full dose of a H2A for more than 2 years might lead to vitamin B_{12} deficiency.[30] In the current study, the incidence of cognitive impairment was significant only in those who used H2As continuously.

This study has a number of limitations. First, the ascertainment of medication use was based on up to three interviews during the 5 years. The study did not have data on the actual medication dispensed during the 5-year follow-up period; thus, continuous use was assumed, although medication use was recorded from direct observation of the medication containers in participants' homes or from active drug lists or was based on informants' reports. Second, the study had few participants who were exposed to H2As (203 in total). Despite the limited power of this study, there was a significant relationship between H2As and incident cognitive impairment. Third, the study population was entirely African American, so generalizability with non-African-American populations is limited. Fourth, the data did not include sufficient information to allow for dose analyses. Despite these limitations, the study had a strong longitudinal design with 5 years of follow-up that allowed for the evaluation of the effect of H2A use on the incidence (but not prevalence) of cognitive impairment in an understudied cohort of African Americans with no prevalence cases of cognitive impairment. In addition, data collection permitted adjustment for potential confounders that might explain the relationship between H2As and cognition.

In conclusion, this study suggests that long-term use of H2As is associated with cognitive impairment in elderly African Americans. Because a significant number of Americans are exposed to H2As every year, with approximately 16 million prescriptions in 2005,[7] the association between H2As and cognitive impairment merits further study. This proposed study would need to measure incident cognitive impairment annually or biannually using a similar accurate methodology of the Indianapolis–Ibadan project and at the same time collect drug dispensing data to capture continuous exposure to certain medications instead of self-reporting at various time points.

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Table 1

Demographics, Medical History, and Baseline Medication Usage According to Participants' Cognitive Status

Characteristic	Preserved Cognition (n = 1,283)	Incident Cognitive Impairment (n = 275)	Test Statistic* (Degrees of Freedom)	*P*-Value
Age, mean ± SD	77.0 ± 6.2	80.6 ± 7.2	−7.58 (366)	<.001
Female, %	66.4	66.5	0.06	1.00
Education, years, mean ± SD	10.1 ± 2.9	9.1 ± 3.2	5.00 (375)	<.001
Baseline cognitive score, mean ± SD†	31.3 ± 1.5	30.5 ± 1.9	6.36 (355)	<.001
Regular alcohol use, %	41.0	35.6	0.01	.10
Hypertension, %	65.6	65.5	0.06	1.00
Diabetes mellitus, %	26.7	21.5	0.01	.08
Stroke, %	10.6	11.6	0.07	.59
Depression, %	7.5	9.8	0.04	.22
Antihyperlipidemia use, %	1.9	1.8	0.19	1.00
Antiplatelet use, %	0.6	0.7	0.30	.69
Aspirin use, %	8.2	7.3	0.09	.71
Benzodiazepine use, %	2.6	2.2	0.16	.83
Medications with definite central anticholinergic activities use, %	8.7	10.9	0.04	.25

*Approximate *t* statistics for continuous values; table probability from Fisher exact test for categorical values.

†From the Community Screening Instrument for Dementia.

SD = standard deviation.

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Table 2

Demographics, Medical History, and Baseline Medication Usage in the Groups Who Used Histamine-2 Receptor Antagonists Continuously and Intermittently and Nonusers

Variable	Continuous Users (n = 38)*	Intermittent Users (n = 165)†	Nonusers (n = 1,355)	Test Statistic (Degrees of Freedom)‡	*P*-Value
Age, mean ± SD	77.7 ± 7.3	77.4 ± 6.0	77.7 ± 6.6	0.08 (2,1555)	.92
Female, %	73.7	78.8	64.7	<0.01	<.001§
Education, years, mean ± SD	9.5 ± 3.1	9.8 ± 3.1	10.0 ± 2.9	0.71 (2,1555)	.49
Baseline cognitive score, mean ± SD¶	30.8 ± 2.0	31.3 ± 1.5	31.2 ± 1.6	1.89 (2,1555)	.15
Regular alcohol use, %	47.4	40.0	39.9	<0.01	.65
Hypertension, %	71.1	72.1	64.6	<0.01	.13
Diabetes mellitus, %	39.5	30.3	24.8	<0.01	.046
Stroke, %	18.4	13.9	10.2	<0.01	.09
Depression, %	18.4	20.0	6.1	<0.01	<.001§,//
Antihyperlipidemia use, %	0.0	3.0	1.8	0.06	.40
Antiplatelet use, %	0.0	1.2	0.6	0.17	.45
Aspirin use, %	10.5	10.3	7.7	0.01	.34
Benzodiazepine use, %	2.6	4.8	2.2	0.01	.10
Medications with definite central anticholinergic activities use, %	21.1	18.2	7.6	<0.01	.02§,//

*Use during all participating waves.

†Use during at least one participating wave but not at all waves.

‡*F* statistic for continuous values; table probability from Fisher exact test for categorical values.

§From the Community Screening Instrument for Dementia.

¶Intermittent and nonusers are significantly different (*P*<.05).

//Continuous and nonusers are significantly different (*P*<.05).

SD = standard deviation.