pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2023;19(6):621-623 / https://doi.org/10.3988/jcn.2023.0172

Association Between Ambroxol at the Usual Dose and the Risk of Parkinson's Disease in Chronic Lung Disease

Min Seung Kim[a*]
Jungkuk Lee[b*]
Dongwoo Kang[b]
Hasung Kim[b]
Suk Yun Kang[a]

[a]Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Korea
[b]Data Science Team, Hanmi Pharm. Co., Ltd, Seoul, Korea

Received May 14, 2023
Revised July 1, 2023
Accepted August 4, 2023

Correspondence
Suk Yun Kang, MD, PhD
Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, 7 Keunjaebong-gil, Hwaseong 18450, Korea
Tel +82-31-8086-2310
Fax +82-31-8086-2317
E-mail sukyunkang@hanmail.net

*These authors contributed equally to this work.

Dear Editor,

Mutation of the glucocerebrosidase (GBA) gene that causes the lysosomal storage disorder called Gaucher disease is known to be the most common genetic risk factor for Parkinson's disease (PD), reportedly being present in 5%−30% of PD patients.[1] The GBA gene encodes the lysosomal enzyme glucocerebrosidase (GCase). GCase activity was negatively correlated with the α-synuclein level, and α-synuclein accumulation has been found to be increased in both GBA cell and animal models.[2] The GCase activity was significantly decreased in the PD brain with GBA gene mutation and in the idiopathic PD brain, suggesting that its activity is closely associated with the pathogenesis of PD.

Ambroxol is a commercially available expectorant that has been suggested to be a disease-modifying drug for PD. Several studies have demonstrated that ambroxol increases GCase activity and decreases α-synuclein levels, and these findings were also demonstrated in PD irrespective of the presence of GBA gene mutation.[2] High-dose ambroxol was effective in halting the progression of Gaucher disease in case studies.[3-5]

While other studies have found ambroxol to be safe when administered at high doses in humans, the safety of long-term high-dose administration still needs to be confirmed. Moreover, there has been no investigation of the effects of administering ambroxol within the approved dose range in the real world. A high dose is defined as a dose that exceeds the permitted dose, and usually higher-than-permitted doses have been administered in previous PD clinical studies (e.g., 1.26 g/day).[2] The usual dose is that permitted in clinical practice (e.g., 90 mg/day according to the Korea Pharmaceutical Information Center at https://www.health.kr/searchDrug/result_drug.asp?drug_cd=2009071505405). We thus aimed to investigate the association between ambroxol at the usual dose and the risk of Parkinson's disease in chronic lung disease (CLD) based on the nationwide Korean National Health Insurance Database (NHID).

We analyzed data extracted from nationwide population-based cohort data from the National Health Insurance Service (NHIS) of the Republic of Korea. The NHIS is a mandatory social health insurance service covering about 97% of the entire Korean population. The characteristics of the data source have been described in detail elsewhere.[6] The Institutional Review Board of Hallym University Dongtan Sacred Hospital approved the study protocol. The study was exempted from needing to obtain informed consents because the data were anonymous and deidentified. All procedures were performed in accordance with the Declaration of Helsinki and followed relevant guidelines and regulations.

The study population and analysis methods are described in detail as supplementary data (Supplementary Materials, Supplementary Fig. 1, and Supplementary Table 1 in the online-only Data Supplement). The demographics of the CLD patients who were and were not ambroxol users are summarized in Supplementary Tables 2 and 3 (in the online-only Data Supplement). The Charlson Comorbidity Index was significantly higher in ambroxol users

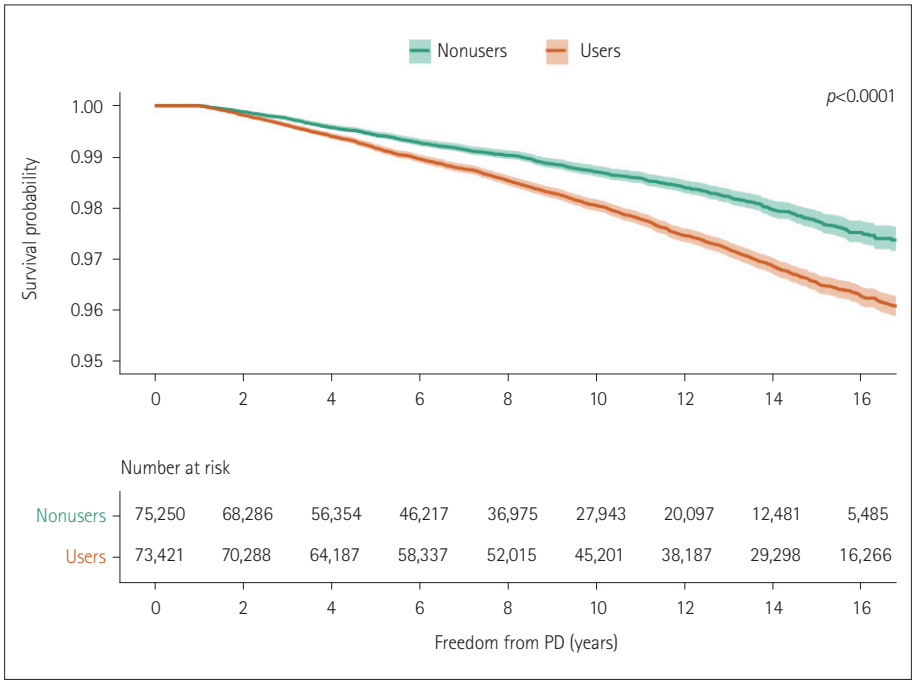

Fig. 1. Kaplan-Meier curves of the freedom from PD for ambroxol users and nonusers. The number of patients at risk over time are shown (p<0.001 by log-rank test). PD, Parkinson's disease.

(p<0.001).

The risk of PD was significantly higher in CLD patients treated with ambroxol than in ambroxol nonusers (adjusted hazard ratio [aHR]=1.383, 95% confidence interval [CI]=1.272–1.504, p<0.0001; Supplementary Table 4 in the online-only Data Supplement). Kaplan-Meier analysis showed that the cumulative incidence of PD was significantly higher in ambroxol users during a 16-year follow-up (p<0.001 in log-rank test; Fig. 1). An analysis of the dose–incidence relationship showed that the risk of PD was highest in ambroxol users with cumulative defined daily doses >15, Supplementary Materials (in the online-only Data Supplement) (aHR=1.624, 95% CI=1.431–1.843, p<0.0001; Supplementary Table 5 in the online-only Data Supplement).

This study found that ambroxol users had a significantly higher PD risk than did ambroxol nonusers. It is possible that the usual dose of ambroxol does not produce any significant effect. As mentioned above, it has been suggested that high-dose ambroxol is effective at modifying PD progression. A previous investigation of nonhuman primates found that GCase activity was increased for ambroxol treatment at 100 mg/day but not at 22.5 mg/day.[7] In transgenic mice, GCase activity increased significantly in a high-dose administration group (ambroxol at a concentration of 4 mM).[8] However, since GCase activity was not increased at the highest dose tested (ambroxol at a concentration of 5 mM), it is not yet known whether higher doses provide more-effective treatments.[8]

Our study found that the incidence of PD was higher in ambroxol users, which is contrary to previous findings. Although adjusted analyses were performed, differences in the number of comorbidities between ambroxol users and nonusers may have been a bias in this study since numerous comorbidities associated with PD have been reported to increase the PD risk.[9] We conducted several sensitivity analyses. It is generally better to maintain the balance of baseline characteristics between two groups by applying propensity-score analysis rather than multivariate analysis (traditional covariate adjustment). However, we also conducted a propensity-score-matching analysis, which produced similar results (Supplementary Tables 6 and 7 in the online-only Data Supplement). Conventional methods for survival analysis ignoring competing events, such as the Kaplan-Meier method and standard Cox proportional-hazards regression, may be inappropriate in the presence of competing risks, when alternative methods specifically designed for analyzing competing-risks data should be applied. Since death is a common competing risk, we also used a subdistribution proportional-hazards model with a competing risk to calculate the risks of PD, which yielded the same results (Supplementary Table 8 in the online-only Data Supplement). We also performed a sensitivity analysis including patients prescribed ambroxol at 1 year after a CLD diagnosis, which also produced similar results (aHR=1.41, 95% CI=1.31–1.52, p<0.0001).

This study had some limitations. First, the NHID contains

data on which drugs were prescribed, which might differ from what patients actually took. Second, confounders such as smoking, alcohol consumption, physical activity, and obesity were not adjusted in this study, and so these factors might have exerted confounding effects. Third, there may have been differences in disease severity, comorbidities, and symptoms between CLD patients who were and were not prescribed ambroxol, which would have influenced the results. Fourth, we did not check that all of the study subjects took ambroxol at the usual dose. However, in clinical practice, it is unlikely that this drug would be prescribed at a dose higher than the approved dose. Fifth, this study involved patients with CLD, and so the results might not apply to individuals without CLD.

In conclusion, the usual dose of ambroxol was associated with an increased risk of PD. Further studies are needed that investigate the risk of PD incidence while more properly controlling for comorbidity.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2023.0172.

Ethics Statement

The Institutional Review Board of Hallym University Dongtan Sacred Heart Hospital approved the study protocol (IRB No. 2022-02-010). Informed consent was exempted because the data were anonymous and de-identified. All methods were performed in accordance with the Declaration of Helsinki and followed relevant guidelines and regulations.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article (and its supplementary information files).

ORCID iDs

Min Seung Kim	https://orcid.org/0000-0003-4397-6612
Jungkuk Lee	https://orcid.org/0000-0003-1874-449X
Dongwoo Kang	https://orcid.org/0000-0002-6250-9908
Hasung Kim	https://orcid.org/0000-0002-2519-6244
Suk Yun Kang	https://orcid.org/0000-0003-4470-3624

Author Contributions

Conceptualization: Suk Yun Kang. Data curation: Min Seung Kim, Jungkuk Lee, Dongwoo Kang, Hasung Kim. Formal analysis: Jungkuk Lee, Dongwoo Kang, Hasung Kim. Supervision: Hasung Kim, Suk Yun Kang. Writing—original draft: Min Seung Kim, Jungkuk Lee, Suk Yun Kang. Writing—review & editing: Suk Yun Kang.

Conflicts of Interest

Suk Yun Kang, contributing editor of the Journal of Clinical Neurology, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Funding Statement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2021R1F1A1051738). This work was also supported by Hallym University Medical Center Research Fund.

Acknowledgements

The authors thank the Data Science Team of Hanmi Pharmacy for their statistical assistance.

REFERENCES

1. Gegg ME, Menozzi E, Schapira AHV. Glucocerebrosidase-associated Parkinson disease: pathogenic mechanisms and potential drug treatments. *Neurobiol Dis* 2022;166:105663.
2. Mullin S, Smith L, Lee K, D'Souza G, Woodgate P, Elflein J, et al. Ambroxol for the treatment of patients with Parkinson disease with and without glucocerebrosidase gene mutations: a nonrandomized, noncontrolled trial. *JAMA Neurol* 2020;77:427-434.
3. Jiang W, Yi M, Maegawa GHB, Zhang H. Ambroxol improves skeletal and hematological manifestations on a child with Gaucher disease. *J Hum Genet* 2020;65:345-349.
4. Kim YM, Yum MS, Heo SH, Kim T, Jin HK, Bae JS, et al. Pharmacologic properties of high-dose ambroxol in four patients with Gaucher disease and myoclonic epilepsy. *J Med Genet* 2020;57:124-131.
5. Narita A, Shirai K, Itamura S, Matsuda A, Ishihara A, Matsushita K, et al. Ambroxol chaperone therapy for neuronopathic Gaucher disease: a pilot study. *Ann Clin Transl Neurol* 2016;3:200-215.
6. Park J, Kim G, Kim H, Lee J, Jin SM, Kim JH. The associations between changes in hepatic steatosis and heart failure and mortality: a nationwide cohort study. *Cardiovasc Diabetol* 2022;21:287.
7. Migdalska-Richards A, Ko WKD, Li Q, Bezard E, Schapira AHV. Oral ambroxol increases brain glucocerebrosidase activity in a nonhuman primate. *Synapse* 2017;71:e21967.
8. Migdalska-Richards A, Daly L, Bezard E, Schapira AH. Ambroxol effects in glucocerebrosidase and α-synuclein transgenic mice. *Ann Neurol* 2016;80:766-775.
9. Santiago JA, Bottero V, Potashkin JA. Biological and clinical implications of comorbidities in Parkinson's disease. *Front Aging Neurosci* 2017;9:394.