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Amiodarone-Associated Optic Neuropathy

A Nationwide Study

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Purpose: To investigate whether amiodarone use is associated with an increased risk of optic neuropathy.

Design: Retrospective population-based cohort study.

Participants: Patients newly treated with amiodarone between 2005 and 2009 were identified from the Taiwan National Health Insurance Research Database. For each case patient, the study also included 4 age- and gender-matched control subjects who did not receive amiodarone treatment.

Methods: Cox multivariate regression analysis was used to assess the association between amiodarone and the occurrence of optic neuropathy.

Main Outcome Measures: Hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The analysis included 6175 amiodarone-treated patients and 24 700 controls. The mean age was 66.7 years and 55.3% of subjects were male. The mean follow-up was 688 days. During the observational period, optic neuropathy developed in 17 amiodarone-treated patients (0.3%) and 30 control patients (0.1%; $P = 0.006$). Multivariate Cox regression analysis showed that amiodarone-treated patients had a 2-fold increased risk of optic neuropathy (HR, 2.09; 95% CI, 1.13−3.85; $P = 0.02$). After stratification by gender, amiodarone use remained a significant factor for optic neuropathy development among male subjects (HR, 3.05; 95% CI, 1.42−6.55; $P = 0.004$), but not among female subjects (HR, 1.15; 95% CI, 0.38−3.47; $P = 0.81$). Among amiodarone-treated patients, male gender was associated with a nearly 3-fold increased risk of optic neuropathy development compared with female gender (HR, 2.91; 95% CI, 0.94−9.01; $P = 0.06$). We also detected a trend of increased cumulative incidence of optic neuropathy with longer treatment duration (>41 vs. ≤41 days; HR, 3.46; 95% CI, 0.99−12.07; $P = 0.05$). However, higher daily dose did not increase the risk of optic neuropathy (HR, 0.96; 95% CI, 0.91−1.00; $P = 0.07$).

Conclusions: These results demonstrated a higher risk of optic neuropathy in patients treated with amiodarone, especially in males and possibly in patients with longer duration of treatment. *Ophthalmology 2015;122:2553-2559 © 2015 by the American Academy of Ophthalmology.*

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The di-iodinated benzofuran derivative amiodarone was developed originally for angina pectoris treatment in the 1960s and currently is one of the most effective and commonly prescribed antiarrhythmic medications worldwide.[1] However, it can have toxic effects on many organs, including the eye, in which corneal deposits, cataracts, and optic neuropathy can develop.[1−3] Amiodarone-associated optic neuropathy includes clinical features similar to those found in nonarteritic anterior ischemic optic neuropathy (NAION), the most common acute optic neuropathy in patients older than 50 years of age.[4] However, in contrast to NAION, amiodarone-associated optic neuropathy tends to have an insidious onset, male preponderance, bilateral involvement, and delayed resolution of disc edema.[5−7]

Studies of amiodarone-associated optic neuropathy reported a mean duration of amiodarone use of 9 months (range, 1−84 months), with most cases commencing within 12 months of initiating amiodarone treatment, and with a median dose of 200 mg (range, 57−1200 mg/day).[5] Visual acuity on diagnosis of amiodarone-associated optic neuropathy ranged from 20/15 to light perception.[5] After discontinuing amiodarone use, 58% of patients achieved visual improvement, whereas 21% ended up with legal blindness at least in 1 eye.[5,8]

Debate persists regarding the existence of amiodarone-associated optic neuropathy. Based on cases reported in the literature, the estimated annual incidence ranges from 0.36% to 2.0%.[9] Based on data from January 1993 through October 2010, the Food and Drug Administration's Adverse Event Reporting System gives a proportional reporting ratio of 4.62, indicating the relative number of reports of amiodarone-associated optic neuropathy compared with those for all medications.[5] However, Mindel et al[10] performed a prospective, randomized study that included more than 1600 subjects with a median follow-up of 45.5 months and did not show any significant correlation between amiodarone and bilateral vision loss. Mindel[11] also used data from the Food and Drug Administration and IMS

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National Prescription Audit to calculate the annual incidence of amiodarone-associated optic neuropathy as 0.0016%, which was lower than the reported incidence of NAION (0.0023%).[11,12] Considering the large population using amiodarone, it is important to clarify the association between amiodarone and optic neuropathy. This study aimed to determine whether amiodarone use was associated with an increased risk of optic neuropathy.

Methods

We conducted a retrospective population-based cohort study using Taiwan's National Health Insurance Research Database (NHIRD). The study included patients who were newly treated with amiodarone between 2005 and 2009. Patients with a history of taking amiodarone before this period or with antecedent optic neuropathy were excluded. For each included case patient, we identified and recruited 4 age- and gender-matched control patients who did not receive amiodarone treatment. We collected data regarding comorbidities, such as hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, cerebrovascular accident, chronic kidney disease, obstructive sleep apnea (OSA), and cancer. Cancer diagnoses were identified from the Catastrophic Illness Registry in NHIRD, which includes only pathologically confirmed cancer cases. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the hospital.

The National Health Insurance (NHI) program in Taiwan is mandatory general health insurance that covers emergency, inpatient, and outpatient care as well as prescription of medication. It covers up to 99% of Taiwan residents.[13] The National Health Research Institutes maintains the NHIRD and releases this information for scientific research. The data are encrypted to prevent identification of any individual patient. In this study, we used the Longitudinal Health Insurance Database of the NHIRD, which is a representative database including 1 000 000 patients randomly selected from the registered beneficiaries of the NHI program.

The primary outcome in this study was the occurrence of optic neuropathy. Diagnosis of optic neuropathy required that the following criteria be met: (1) an optic neuropathy diagnostic code, that is, International Classification of Diseases, Ninth Revision, Clinical Modification codes 377, 377.1, 377.2, 377.3 through 377.39, 377.4, 377.41, 377.49, 377.9, 950, 950.0, or 950.9; (2) visual field examination on the day of diagnosis; and (3) having undergone a fundus examination, such as funduscopy, indirect ophthalmoscopy, fundus color photography, or fluorescein angiography. All case and control subjects were followed up until the development of optic neuropathy, death, drop-out from the NHI program, or the end of 2 years of follow-up.

The secondary outcome was to determine whether the amiodarone daily dose or treatment duration affected the development of optic neuropathy. The average daily dose of amiodarone was calculated as the total amiodarone dose divided by the duration of amiodarone use.

Statistical Analysis

Descriptive statistics included the mean and standard deviation (SD) for continuous variables and the number and percentage for categorical variables. The association between each clinical variable and the occurrence of optic neuropathy was evaluated initially using univariate analysis. In the univariate analysis, variables with a P value less than 0.05 were adjusted in the multivariate Cox regression model. In addition, age, gender, and amiodarone use were forced to be part of the multivariate model. The analysis was stratified further by gender to identify any possible gender differences. We also used a Cox regression model to analyze the impact of amiodarone daily dose and treatment duration on the occurrence of optic neuropathy.

Data extraction, processing, and sampling were performed using the Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, WA). SPSS for Windows software version 18 (SPSS, Inc., Chicago, IL) was used for statistical analysis. All reported P values were based on 2-sided tests, and a P value less than 0.05 was considered to be statistically significant.

Results

We identified 6772 patients treated with amiodarone, of whom 597 were excluded because of a history of taking amiodarone before the study period. Thus, the study included a total of 6175 patients who were newly treated with amiodarone, along with 24 700 age- and gender-matched control subjects. The mean age of all study subjects was 66.7 years (SD, 14.9 years; range, 17−107 years), and 55.3% of subjects were male. The mean follow-up was 688 days (SD, 142 days; range, 1−731 days). Compared with the controls, patients treated with amiodarone had a higher proportion of medical comorbidities, including hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, cerebrovascular event, chronic kidney disease, OSA, and cancer (Table 1). During the observational period, optic neuropathy was diagnosed in 17 amiodarone-treated patients (0.3%) and 30 control patients (0.1%; $P = 0.006$).

On the Kaplan-Meier curve, the optic neuropathy−free survival rate differed significantly between the amiodarone group and

Table 1. Characteristics of Amiodarone-Treated Patients and Control Subjects

	Amiodarone-Treated Patients (n = 6175)	Controls (n = 24 700)
Age (yrs)		
Mean±standard deviation	66.8±14.9	66.7±14.9
Range	18−102	17−107
Male gender, no. (%)	3416 (55.3%)	13 668 (55.3%)
Medical comorbidities, no. (%)		
Diabetes mellitus*	1582 (25.6%)	3834 (15.5%)
Hypertension*	3654 (59.2%)	9320 (37.7%)
Dyslipidemia*	1330 (21.5%)	3386 (13.7%)
Coronary artery disease*	2200 (35.6%)	4457 (18.0%)
Cerebrovascular event*	1061 (17.2%)	2473 (10.0%)
Chronic kidney disease*	456 (7.4%)	728 (2.9%)
Obstructive sleep apnea syndrome*	23 (0.4%)	25 (0.1%)
Cancer*	695 (11.3%)	1589 (6.4%)
Occurrence of optic neuropathy, no. (%)†	17 (0.3%)	30 (0.1%)
Days of follow-up*		
Mean±standard deviation	1130±710	2421±528
Range	1−2553	1−2555

Continuous variables are presented as mean±standard deviation (range) and compared using the Student t test. Categorical variables are presented as number (percentage) and compared using Pearson's chi-square test.
*$P < 0.001$.
†$P < 0.01$.