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Association of amiodarone use with acute pancreatitis in patients with atrial fibrillation: a nested case-control study

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Amiodarone is an antiarrhythmic frequently used in the treatment of atrial fibrillation (AF). Isolated reports have suggested that use of amiodarone may cause acute pancreatitis.[1–3] This potential adverse effect of amiodarone has not been explored in large studies. We assessed whether use of amiodarone or other antiarrhythmics indicated for AF management is associated with developing acute pancreatitis in a large US population.

METHODS

We conducted a case-control study nested in the Truven Health MarketScan® Commercial Database and the Medicare Supplemental Database for the period January 1, 2007 to December 31, 2012. These databases include health insurance claims spanning all levels of care (inpatient and outpatient services, outpatient pharmacy services) and enrollment data from employers and health plans across the US providing private coverage for employees, their spouses, dependents, and individuals and their dependents with Medicare supplemental coverage.

Cases were patients with non-valvular AF (NVAF) admitted to the hospital with a primary diagnosis of acute pancreatitis during the study period (ICD-9-CM code 577.0). Five controls with NVAF were matched with each case by sex, year of birth, and MarketScan enrollment date selected from individuals enrolled at the time of the pancreatitis hospitalization in the case (index date). Information on use of amiodarone, other medications, and comorbidities prior to the index date for cases and controls was obtained. We used multivariable conditional logistic regression to estimate odds ratios (OR) and 95%

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Dr. Alonso, at the University of Minnesota, conducted the data analysis, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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confidence intervals (95%CI) of acute pancreatitis by use of amiodarone and other antiarrhythmics (each using separate regression models), and time since initiation and cumulative use of amiodarone adjusting for confounders (listed in Table 1).

RESULTS

We included 1686 cases and 8430 matched controls (39% women, 71 mean age, Table 1). Ever users had an increased odds of acute pancreatitis compared to never users (Table 2), particularly when amiodarone was initiated within 12 months prior to the event date: multivariable OR (95%CI) 1.86 (1.41–2.45) versus 1.21 (0.89–1.64) if >12 months since initiation (p=0.04 for the difference between the two ORs) compared to never users. Cumulative use was not associated with increased odds of acute pancreatitis (p for trend among users=0.49). Use of other antiarrhythmics was not associated with acute pancreatitis (Table 2).

DISCUSSION

In this study of healthcare utilization data, use of amiodarone, but not of other anti-arrhythmics, was associated with a 50% increased odds of acute pancreatitis among patients with NVAF. The odds were almost doubled in the 12 months after amiodarone initiation and did not depend on cumulative use of amiodarone. Considering an incidence of acute pancreatitis of 3–4 cases per 10,000 adults per year,[4] the observed association would result in approximately 1–2 additional cases of acute pancreatitis per 10,000 amiodarone users per year. A few isolated case reports of acute pancreatitis possibly linked to amiodarone use have been described in the literature.[1–3] The mechanisms responsible for this association are unknown, though direct cytotoxicity or immune-mediated pathways, as described for amiodarone-related pulmonary toxicity, could be potential explanations.[5]

Strengths of our study include the prospective assessment of medication use, the large sample size, and the availability of information on comorbidities and use of other medications potentially associated with increased risk of acute pancreatitis. Limitations are related to the use of healthcare utilization data: limited information on the validity of claims for acute pancreatitis; absence of clinical variables characterizing severity of the episode (e.g. blood markers of acute pancreatitis); and the select group of patients included in this database.

Our results indicate that acute pancreatitis could be an adverse effect of amiodarone use, an effect that may not be shared by other anti-arrhythmics. Even though the absolute risk of acute pancreatitis in the general population is low, clinicians should be aware of this potential relationship in the management of patients with NVAF or acute pancreatitis. Further research should replicate our findings and determine potential mechanisms.

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Table 1

Selected characteristics of cases and controls, MarketScan 2007–2012

	Cases (N = 1686)	Controls (N = 8430)
Age, years	71 (14)	71 (14)
Women, %	39	39
History of gallbladder disease, %	42	4
Alcoholism, %	5	1
Hypertriglyceridemia, %	3	1
Prior pancreatic disease, %	21	1
History of diabetes, %	40	27
Prior use of:		
Azatiophrine, %	0.4	0.3
Mercaptopurine, %	0.1	0.1
Sulfonamides, %	15	11
Tetracyclines, %	13	9
Valproic acid, %	0.1	0.1

Values refer to mean (standard deviation) or percentage

Table 2

Odds ratios (OR) and 95% confidence interval (95% CI) of acute pancreatitis by previous use of selected antiarrhythmic drugs in patients with non-valvular atrial fibrillation (1686 cases and 8430 controls), MarketScan 2007–2012

	Exposed cases N (%)	Exposed controls N (%)	OR	95%CI
Amiodarone	245 (14.5)	758 (9.0)	1.53	1.24–1.88
Dronedarone	38 (2.3)	186 (2.2)	0.97	0.61–1.53
Sotalol	103 (6.1)	457 (5.4)	0.95	0.71–1.27
Flecainide	56 (3.3)	286 (3.4)	0.88	0.60–1.29
Propafenone	59 (3.5)	262 (3.1)	1.18	0.80–1.74
Dofetilide	10 (0.6)	65 (0.8)	0.46	0.17–1.22

Conditional logistic regression adjusted for matching factors, age at index date, history of gallbladder disease, alcoholism, hypertriglyceridemia, diabetes, other pancreatic disease, or cholestatic disease, and prior use of azathioprine, mercaptopurine, sulfonamides, tetracyclines, or valproic acid.