

ORIGINAL RESEARCH ARTICLE

Risk of Arrhythmias Associated with Ipratropium Bromide in Children, Adolescents, and Young Adults with Asthma: A Nested Case-Control Study

Sruthi Adimadhyam,¹ Glen T. Schumock,^{1,2,3} Surrey Walton,^{1,3} Min Joo,⁴ Joanne McKell,⁴ and Todd A. Lee^{1,2,3,4,*}

¹Department of Pharmacy Systems Outcomes and Policy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois; ²Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois; ³Center for Pharmacoepidemiology and Pharmacoeconomic Research, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois; ⁴Section of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois

STUDY OBJECTIVE To evaluate the risk of arrhythmias associated with inhaled anticholinergic (IAC) use in young patients with asthma.

DESIGN Population-based nested case-control study.

DATABASE IMS LifeLink Health Plan Claims Database.

PATIENTS Patients 5–24 years of age who were diagnosed with asthma and were new users of asthma controller medications were identified between July 1997 and April 2010. Cases were newly diagnosed with arrhythmia and were matched with up to 10 controls based on age, gender, geographic region, and quarter and year of first controller medication dispensing.

MEASUREMENTS AND MAIN RESULTS Exposure to IACs was determined in the 180 days prior to the event date, defined as date of arrhythmia claim. Active use was defined as sufficient days' supply of a prescription to extend through the event date. Among 283,429 patients with asthma, 7656 cases were matched to 76,304 controls. Most of those included were female (58.8%) and 12 years or older (73.3%). Active exposure of IACs was observed in 0.69% of cases and 0.18% of controls. Active use was associated with a 1.56-fold increase in arrhythmia risk compared with nonactive users or non-users (adjusted odds ratio [OR_{adj}] 1.56, 95% confidence interval [CI] 1.08–2.25). Risk was highest among active users of ipratropium (OR_{adj} 1.59, 95% CI 1.08–2.33). Active high-dose users of IACs (more than 0.114 mg of ipratropium equivalents) had a 69% increase in risk (OR_{adj} 1.69, 95% CI 1.10–2.59), whereas the added risk for active users receiving low-dose IACs (0.114 mg of ipratropium equivalents or less) was not statistically significant (OR_{adj} 1.22, 95% CI 0.53–2.65).

CONCLUSION Use of ipratropium bromide was associated with an increased risk of arrhythmias in 12–24-year-old patients with asthma.

KEY WORDS asthma management, ipratropium bromide, arrhythmias, nested case-control design. (Pharmacotherapy 2014;34(4):315–323) doi: 10.1002/phar.1336

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*Address for correspondence: Todd A. Lee, UIC Center for Pharmacoepidemiology and Pharmacoeconomic Research, University of Illinois at Chicago, 833 S. Wood Street, Room 164 M/C 886, Chicago, IL 60612; e-mail: toddlee@uic.edu.

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Asthma affects 20.5 million adults and 6.5 million children in the United States, resulting in more than 497,000 hospitalizations and 1.8 million emergency department visits annually.¹ With a prevalence of 9.6% in children 5–17 years of age, asthma is the most common chronic condition in the pediatric population.¹ The National Asthma Education and Prevention

Program guidelines recommend inhaled corticosteroids (ICS) in combination with long-acting β -agonists (LABAs) as treatment for patients with moderate to severe persistent asthma.² However, concerns about LABA safety, particularly when used without ICS, highlight the importance of examining alternative therapies for asthma treatment.^{3, 4}

Inhaled anticholinergics (IACs) are bronchodilators of choice in the management of chronic obstructive pulmonary disease (COPD). Use of IACs for chronic management of asthma is currently not approved by the U.S. Food and Drug Administration. However, several studies, including the Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroids (TALC) study, have shown that IACs may offer an alternative to a regimen of LABA and ICS in asthma.^{5, 6} Despite perceived safety, IACs have been associated with systemic adverse effects including dry mouth, urinary retention, and tachycardia.⁷ Tachycardia and other forms of arrhythmia are of particular importance because they might precipitate other cerebrovascular and cardiovascular adverse events.⁸ Recent studies in patients with COPD found that IAC use was associated with increased cardiovascular adverse events including stroke, myocardial infarction, and death.^{9–14} However, there is contradictory evidence regarding this association in the published literature. Although there are some clinical trials, meta-analyses, and observational studies that show a positive association, an equal number show the contrary. Lack of evidence backed by a well-designed trial limits our understanding of the true association. The methodological limitations of each of the studies conducted thus far are highlighted elsewhere.¹⁵ Moreover, data existing in the literature pertain to the use of IACs among the adult population.

The cardiovascular risk of IACs in a young asthma population is unknown and might be different than the risk observed in an older COPD population because the COPD population shares cardiovascular disease risk factors such as advanced age and smoking tobacco. Further, the baseline absolute risk of serious cardiac events in pediatric, adolescent, and young adult populations is low and not likely to be detected in clinical trials. Hence the use of observational data is important in assessing whether IAC use in asthma is associated with increased cardiovascular risk. Thus the objective of this study was

to investigate the association between IAC use and arrhythmias in young patients with asthma.

Methods

This nested case-control study was conducted within a cohort of children, adolescents, and young adults with asthma identified in a commercial health insurance claims database. Because the institutional review board (IRB) at the University of Illinois at Chicago determined that this study was not human subjects research, IRB approval was not needed.

Data Source

Data were obtained from the IMS LifeLink Health Plan Claims Database (IMS Health Inc., Danbury, CT). The database consisted of medical and pharmaceutical claims for more than 60 million patients across the United States. The database included demographic information (e.g., age, gender, and geographic region), dates of enrollment, inpatient and outpatient diagnoses, medical procedures, and prescriptions dispensed.

Study Cohort

The study cohort consisted of patients who had an asthma diagnosis (*International Classification of Diseases, Ninth Revision* (ICD-9) code 493.xx) between July 1, 1997, and April 30, 2010, followed by a first-time prescription for an asthma controller medication. Controller medications included ICS, LABAs, leukotriene-modifying agents, xanthines, immunomodulators, mast cell stabilizers, and IACs. The index prescription date was defined as the date each patient first received a controller medication. The cohort was limited to those 5–24 years of age on their index date. Patients were excluded if they were not continuously enrolled for at least 6 months prior to the index prescription date, had a history of arrhythmia, or had congenital heart disease. Starting from their index prescription date, patients were followed until the first event of arrhythmia or the last date of enrollment.

Identification of Cases and Controls

A case was identified based on an outpatient visit, or emergency department visit, or hospitalization with an arrhythmia diagnosis (ICD-9

codes 427.xx, 785.0, 785.1, and 798.xx) during follow-up.¹⁶ The arrhythmia claim date was defined as the event date. Events were categorized as severe or nonsevere. Severe events were inpatient hospitalizations or emergency department visits with an arrhythmia diagnosis. Although the primary analysis included all events, sensitivity analyses included stratification by event severity.

Potential controls were selected by using an incidence density sampling approach where all patients who had not yet experienced an event and were at risk (i.e., event free and not censored) on the event date of the corresponding case were eligible to be sampled as a control. Up to 10 controls were randomly matched from the at-risk population based on category of age (5–11 years or 12–24 years of age), sex, geographic region, and cohort entry quarter and year and assigned the case's event date.^{17, 18}

IAC Exposure

Exposure to IACs was determined in the 180 days before the event date. Based on exposure to any IAC, patients were classified as active users (sufficient days' supply to cover the event date), immediate past users (prescription ended 1–30 days before event date), past users (prescription ended 30–180 days before event date), or nonusers (no prescription in 180 days before event date).

To standardize the measurement of dose across IAC drugs (ipratropium and tiotropium) and formulations, milligrams of ipratropium equivalents were calculated for active exposure. The total dose of tiotropium was determined by multiplying the quantity dispensed per prescription by the milligrams in each capsule. This dose was converted to ipratropium equivalents using a conversion factor of 7.5, which was obtained by equating the recommended daily doses of ipratropium (0.136 mg) and tiotropium (0.018 mg) in COPD because tiotropium is not indicated for use in asthma. Asthma patients in the TALC study were also given tiotropium at a dose recommended for COPD.⁵ For ipratropium metered-dose inhalers, the total number of puffs was determined by multiplying the number of canisters (quantity dispensed/package size) with the number of puffs per canister. The total dose was calculated by multiplying the total the number of puffs by the amount of ipratropium per puff. For nebulizers, the total dose was calculated by multiplying quantity dispensed by the

solution strength. The average daily dose was calculated and categorized into low dose (0.114 mg or less of ipratropium equivalents) and high dose (more than 0.114 mg of ipratropium equivalents). The high-dose group was exposed to more than 0.114 mg of ipratropium equivalents, which equates to 6.3 inhalations on average per day. Exposure to individual IACs was also identified.

Covariates

Potential confounders were identified in the 180 days prior to the event date. These included comorbidities associated with arrhythmia (i.e., hyperthyroidism, rheumatic fever, obesity, myocarditis, cardiomyopathy, and ischemic heart disease)^{19–21}; concomitant active use of other asthma medications (i.e., short-acting β -agonists [SABAs], oral corticosteroids, ICS, LABAs, leukotriene-modifying agents, mast cell stabilizers, immunomodulators, and xanthines); concomitant active use of medications with anticholinergic effects (i.e., antiarrhythmic agents, antibacterials, antidepressants, antiemetics, antihistamines, antimalarial agents, antimigraine agents, antipsychotics, calcium channel blockers, cough, cold, and allergy medications, and opioid analgesics)^{22, 23}; and severity of asthma. Severity of asthma in the 180 days prior to the event date was assessed by using previously established proxy measures including number of asthma-related emergency department visits, number of SABA canisters dispensed, use of oral corticosteroids, and number of acute asthma exacerbations.^{24, 25} Acute asthma exacerbations were identified by a prescription for oral corticosteroids filled within 7 days of an outpatient encounter for asthma.

Statistical Analysis

The association between IACs and arrhythmias expressed as an odds ratio (OR) with 95% confidence interval (95% CI) was determined by using multivariate conditional logistic regression. In developing adjusted models, all covariates associated with both exposure and outcome in univariate analyses were first selected. Covariates that modified the OR estimate for exposure to IACs by 10% or more were included in the final model.²⁶ Covariates in the final model included asthma severity measures (number of asthma-related emergency department visits, number of acute exacerbations, use of oral corticosteroids,

number of SABA canisters), concomitant use of other asthma medications (SABAs, ICS, oral corticosteroids), comorbid conditions (ischemic heart disease, cardiomyopathy), and concomitant use of systemic drugs with anticholinergic effects (antibacterials, antidepressants, cough, cold, and allergy medications, opioid analgesics). Separate analyses were conducted to determine OR estimates for exposure to ipratropium, tiotropium, and combination (ipratropium-albuterol) anticholinergics. All statistical analyses were conducted by using Stata, v.11.0 (StataCorp, College Station, TX).

Sensitivity Analyses

Several sensitivity analyses were conducted to evaluate the robustness of the study results. First, separate analyses of severe and nonsevere events were conducted. Second, patients who switched to IACs after using SABAs in the immediate past were excluded because of concern that prescribers may have switched these patients because of symptoms suggesting SABA-associated palpitations. The association in severe and nonsevere events excluding immediate past SABA users was reassessed. Third, in response to differences in prevalence of cardiovascular risk factors between cases and controls, patients with ischemic heart disease and cardiomyopathy were excluded. Last, the cohort was stratified by age category.

Results

A total of 283,429 patients met the inclusion criteria. Within this cohort, 7656 cases were matched to 76,304 controls (Figure 1). The analytic population was mostly female (58.8%) and 12 years or older (73.3%) (Table 1). The median duration of follow-up was 458 days (interquartile range 180–913 days). During follow-up, the incidence rate of arrhythmia was 1.45 cases per 10,000 person-days. Cases were more likely to have comorbidities that increased arrhythmia risk, more likely to have severe asthma, and more commonly receiving systemic drugs with anticholinergic effects.

The top five arrhythmia diagnoses among cases were palpitations (35.5%; ICD-9 code 785.0), tachycardia (24.8%; ICD-9 code 785.1), cardiac dysrhythmia (17.8%; ICD-9 code 427.9), other rhythm disorders (14.5%; ICD-9 code 427.89), and sinoatrial node dysfunction (1.5%; ICD-9 code 427.81). There were seven cases

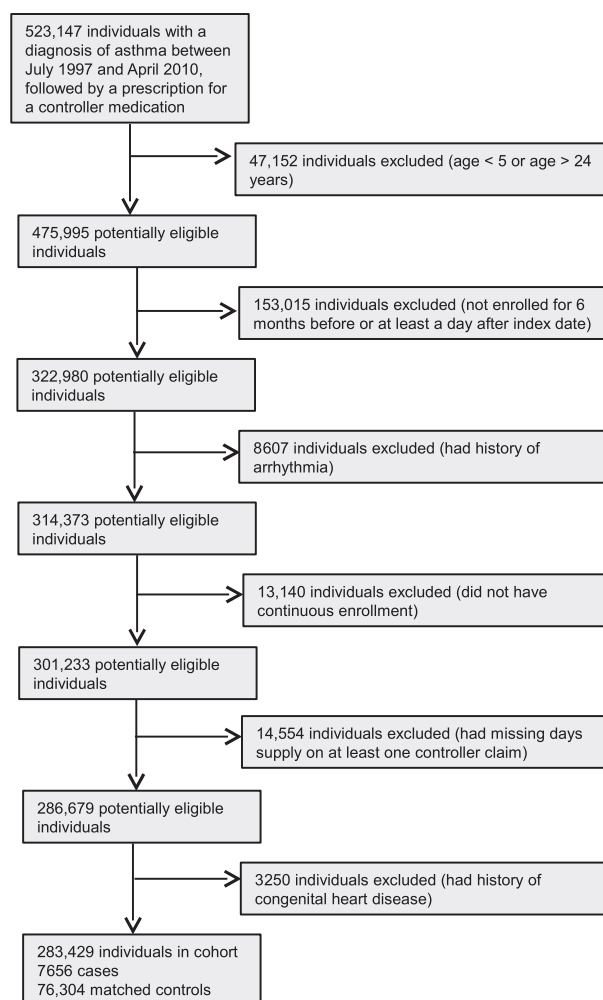


Figure 1. Schematic of the patient selection process for the study cohort. Data from IMS Health, LifeLink™ Health Plan Claims Database, From 1997 to 2010.

(0.09%; ICD-9 code 798.xx) of sudden/instantaneous death. Most of the events (83.1%) were identified from outpatient visits; the remainder were hospitalizations (8.9%) or emergency department visits (8.0%).

Overall IAC exposure was small, with 0.69% of cases and 0.18% of controls having active exposure (Table 2). Ipratropium was the predominantly used IAC with active exposure in 0.65% of cases and 0.16% of controls. Active exposure to tiotropium was observed in 0.04% of cases and 0.02% of controls. Among active users of any IAC, 0.53% of cases and 0.12% of controls used a high average daily dose (more than 0.114 mg of ipratropium equivalents).

Compared with nonusers, active users of IACs were at increased risk of arrhythmia (adjusted odds ratio [OR_{adj}] 1.56, 95% CI 1.08–2.25) (Table 2). Those in the high-dose group were at

Table 1. Characteristics of Analytic Population

Characteristic	Cases (n, %) (n=7656)	Controls (n, %) (n=76,304)	OR _{unadjusted} (95% CI)
Age, yrs			
5–11	2044 (26.7)	20,406 (26.7)	–
12–24	5612 (73.3)	55,898 (73.26)	–
Sex			
Male	3155 (41.21)	31,448 (41.21)	–
Female	4501 (58.79)	44,856 (58.79)	–
Comorbidities			
Hyperthyroidism	49 (0.64)	102 (0.13)	4.81 (3.42–6.78)
Rheumatic fever	7 (0.09)	12 (0.02)	5.07 (1.96–13.14)
Obesity	296 (3.87)	1317 (1.73)	2.30 (2.02–2.62)
Myocarditis	2 (0.03)	2 (0.0026)	10 (1.40–70.99)
Ischemic heart disease	60 (0.78)	50 (0.07)	12.16 (8.33–17.74)
Cardiomyopathy	27 (0.35)	11 (0.01)	24.54 (12.17–49.48)
Markers of asthma severity			
Emergency department visits			
0	5492 (71.73)	64,205 (84.14)	Reference
< 6	1828 (23.88)	10,946 (14.35)	1.99 (1.88–2.11)
≥ 6	336 (4.39)	1153 (1.51)	3.62 (3.18–4.11)
SABA canisters			
< 6	7500 (97.96)	75,183 (98.53)	Reference
≥ 6	156 (2.04)	1121 (1.47)	1.39 (1.17–1.65)
OCS use	1507 (19.68)	9710 (12.73)	1.72 (1.62–1.83)
Number of acute exacerbations			
0	6581 (85.96)	70,261 (92.08)	Reference
< 6	577 (7.54)	4564 (5.98)	1.40 (1.28–1.53)
≥ 6	498 (6.5)	1479 (1.94)	3.75 (3.37–4.18)
Concomitant use of asthma medications			
SABA	1144 (14.94)	6613 (8.67)	1.97 (1.83–2.11)
OCS	344 (4.49)	578 (0.76)	6.64 (5.77–7.64)
ICS	909 (11.87)	6757 (8.86)	1.48 (1.36–1.60)
LABA	496 (6.48)	3776 (4.95)	1.37 (1.23–1.51)
LTMA	680 (8.88)	5391 (7.07)	1.30 (1.19–1.42)
MCS	13 (0.17)	107 (0.14)	1.21 (0.68–2.17)
Immunomodulators	2 (0.03)	9 (0.01)	2.22 (0.48–10.28)
Xanthines	4 (0.05)	24 (0.03)	1.67 (0.58–4.80)
Concomitant use of drugs with anticholinergic effects			
Antiarrhythmic agents	1 (0.01)	0 (0)	–
Antibacterial agents	835 (10.91)	3537 (4.64)	2.57 (2.37–2.80)
Antidepressants	701 (9.16)	2623 (3.44)	2.87 (2.63–3.14)
Antiemetics	39 (0.51)	38 (0.05)	10.62 (6.75–16.71)
Antihistamines	506 (6.61)	3679 (4.82)	1.41 (1.28–1.55)
Antimalarial agents	11 (0.14)	56 (0.07)	1.89 (0.98–3.63)
Antimigraine agents	35 (0.46)	106 (0.14)	3.30 (2.25–4.83)
Antipsychotics	171 (2.23)	470 (0.62)	3.71 (3.10–4.43)
Calcium channel blockers	23 (0.30)	48 (0.06)	4.79 (2.91–7.87)
Cough, cold, and allergy medications	264 (3.45)	1416 (1.86)	1.91 (1.67–2.19)
Opioid analgesics	199 (2.60)	466 (0.61)	4.36 (3.68–5.15)

OR = odds ratio; CI = confidence interval; SABA = short-acting β -agonists; OCS = oral corticosteroids; ICS = inhaled corticosteroids; LABA = long-acting β -agonists; LTMA = leukotriene-modifying agents; MCS = mast cell stabilizers. Data from IMS Health, LifeLink™ Health Plan Claims Database, from 1997 to 2010.

the highest risk for arrhythmia (OR_{adj} 1.69, 95% CI 1.10–2.59), whereas the risk in the low-dose group was not statistically significant (OR_{adj} 1.22, 95% CI 0.53–2.65) compared with nonusers. The sample size of the active tiotropium users was too low to determine if the risk of arrhythmia differed by a specific anticholinergic. However, the risk observed in ipratropium monotherapy users (OR_{adj} 1.59, 95% CI 1.08–2.33) was higher than that observed in combina-

tion ipratropium-SABA users (OR_{adj} 1.20, 95% CI 0.74–1.94) who did not have a statistically significant elevated risk.

The increased risk of arrhythmia in active users of IACs found in the main analysis was consistent across various sensitivity analyses (Figure 2). Active use of IAC had a higher magnitude of increased risk of arrhythmia in severe events (OR_{adj} 3.39, 95% CI 1.39–8.24) compared with nonsevere events (OR_{adj} 1.38, 95% CI

Table 2. Exposure to Inhaled Anticholinergics and the Risk of Arrhythmia

Exposure	Cases (n, %) (n=7656)	Controls (n, %) (n=76,304)	OR _{unadjusted} (95% CI)	OR _{adjusted} (95% CI)
Exposure to IACs				
Nonusers	7502 (97.98)	75,595 (99.07)	Reference	Reference
Active users	53 (0.69)	137 (0.18)	3.95 (2.86–5.44)	1.56 (1.08–2.25)
Immediate past users	32 (0.42)	154 (0.20)	2.10 (1.43–3.09)	1.24 (0.82–1.87)
Past users	69 (0.9)	418 (0.55)	1.66 (1.28–2.15)	1.16 (0.88–1.52)
Exposure to ipratropium monotherapy				
Nonusers	7511 (98.10)	75,633 (99.12)	Reference	Reference
Active users	50 (0.65)	125 (0.16)	4.08 (2.92–5.68)	1.59 (1.08–2.33)
Immediate past users	29 (0.38)	146 (0.19)	2.00 (1.34–3.00)	1.16 (0.75–1.79)
Past users	66 (0.86)	400 (0.52)	1.66 (1.27–2.16)	1.15 (0.87–1.52)
Exposure to combination IACs				
Nonusers	7573 (98.91)	75,853 (99.40)	Reference	Reference
Active users	28 (0.37)	94 (0.12)	3.01 (1.96–4.60)	1.20 (0.74–1.94)
Immediate past	18 (0.24)	104 (0.14)	1.74 (1.05–2.88)	1.02 (0.60–1.75)
Past users	37 (0.48)	253 (0.33)	1.47 (1.03–2.08)	1.05 (0.73–1.52)
Dose of active IAC exposure				
Not exposed	7605 (99.33)	76,171 (99.82)	Reference	Reference
Low-dose (≤ 0.114 mg of ipratropium equivalents)	10 (0.13)	40 (0.05)	2.55 (1.27–5.11)	1.22 (0.53–2.65)
High-dose (> 0.114 mg of ipratropium equivalents)	41 (0.53)	93 (0.12)	4.50 (3.10–6.52)	1.69 (1.10–2.59)

OR = odds ratio; CI = confidence interval; IAC = inhaled anticholinergic.

Effect estimates were adjusted for asthma severity (number of short-acting β -agonist [SABA] canisters dispensed, number of asthma-related emergency department visits, number of acute exacerbations, use of oral corticosteroids in the 180 days before the event date); concomitant use of SABAs, inhaled corticosteroids, oral corticosteroids, antibiotics, antidepressants, cold and allergy medications, opioid analgesics; ischemic heart disease; cardiomyopathy. Data from IMS Health, LifeLink™ Health Plan Claims Database, from 1997 to 2010.

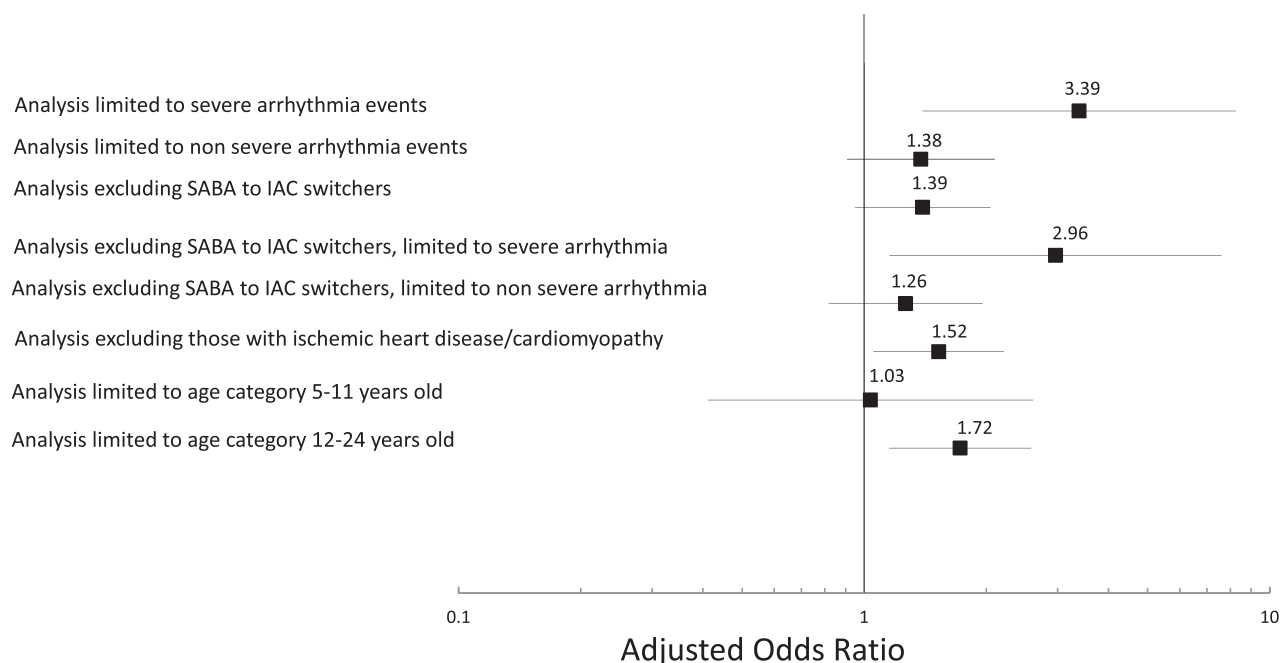


Figure 2. Risk of arrhythmia in the sensitivity analyses. IAC = inhaled anticholinergic; SABA = short-acting β -agonists. Data from IMS Health, LifeLink™ Health Plan Claims Database, from 1997 to 2010.

0.91–2.10). When SABA to IAC switchers were excluded (11 patients: 5 cases, 2 severe, 3 non-severe, and 6 controls), active users of IAC did not have a statistically significant increased risk of arrhythmia (OR_{adj} 1.39, 95% CI 0.95–2.04). The magnitude of effect differed in severe and nonsevere events, with active exposure in severe

events having a larger effect (OR_{adj} 2.96, 95% CI 1.15–7.60) than in nonsevere events (OR_{adj} 1.26, 95% CI 0.82–1.96).

Excluding patients with ischemic heart disease or cardiomyopathy, the OR_{adj} for active use was 1.52 (95% CI 1.05–2.21). When stratifying by age, we found a higher magnitude of increased

risk among patients 12–24 years of age (OR_{adj} 1.72, 95% CI 1.15–2.57) compared with those 5–11 years of age (OR_{adj} 1.03, 95% CI 0.41–2.60).

Discussion

In a cohort of patients 5–24 years of age with asthma who were new users of controller medicines, it was found that active use of IACs was associated with an increased risk of arrhythmia. The effect was stronger in patients 12–24 years of age and was more strongly associated with severe cases of arrhythmia. Further, among patients actively exposed to IACs, those with higher average daily doses were at a greater risk for arrhythmia. Active users of ipratropium were at a higher risk (OR_{adj} 1.59, 95% CI 1.08–2.33) than those using combination ipratropium-SABA (OR_{adj} 1.20, 95% CI 0.74–1.94). However, sample size was limited with respect to tiotropium use.

Results from this study are consistent with literature reporting a positive association between use of IACs and cardiovascular-related adverse events and deaths in patients with COPD. The Lung Health Study reported an increase in supraventricular tachycardia and cardiovascular deaths ($p=0.027$) among smokers randomized to smoking cessation and ipratropium bromide compared with placebo.⁹ A retrospective cohort study of patients with newly diagnosed COPD¹³ reported a 29% increase in the risk of acute coronary syndrome, heart failure, or dysrhythmia (adjusted hazard ratio 1.29, 95% CI 1.21–1.38) associated with anticholinergic exposure. A systematic review¹⁰ reported a higher frequency of arrhythmias in tiotropium exposed compared with placebo (OR 2.33, 95% CI 1.11–4.88). A meta-analysis reported an increased risk of myocardial infarction (OR_{adj} 1.52, 95% CI 1.04–2.22) and cardiovascular death (OR_{adj} 1.92, 95% CI 1.23–3.00) among COPD patients using IACs.¹⁴ However, these studies were conducted in COPD patients with inherent cardiovascular risk factors such as advanced age and smoking histories. The current study examined the association between IACs and arrhythmias in a younger population with asthma who were at a considerably lower risk for cardiovascular diseases. The fact that an increased risk was observed lends creditability to a potential drug effect.

SABAs are the bronchodilators of choice in asthma. It has been shown that some people are more prone to experiencing the cardiovascular effects of β -agonists compared with others due

to a genetic polymorphism.^{27–29} Therefore, patients who switched to IAC therapy from SABAs could potentially be systematically different than those who remained on SABAs, with differences in the polymorphism noted previously or other differences between the groups. Specifically, we were concerned that any effect observed with anticholinergics may be due to confounding by indication, where those patients using IACs were at highest risk. This may be particularly true among patients switched to an IAC because they may have experienced cardiovascular adverse effects from their SABA. To evaluate this, patients switching from SABAs to IACs were excluded, which led to a 17% reduction in the effect estimate. This does not exclude the possibility of confounding by indication explaining the results. However, when this was repeated for severe versus nonsevere cases, severe cases were still found to have a significantly elevated risk associated with active exposure to IACs, reinforcing the potential anticholinergic drug effect.

The findings in this study are particularly important given recent efforts that focused on evaluating tiotropium efficacy in treating patients with asthma. The TALC study found that combination tiotropium and ICS was superior to doubling the dose of ICS but not inferior to combination LABA and ICS.⁵ Although the TALC results are promising from an efficacy standpoint, the sample size is inadequate for alleviating potential safety concerns associated with anticholinergic treatment in patients with asthma. Given the event rate observed in this analysis and that TALC included 174 patients, it is not surprising there were not any cardiovascular adverse events reported in the TALC study. Although the current investigation was observational, it was conducted using a large population-based data set that included a broader range of patients and a longer duration of follow-up compared with randomized controlled trials investigating the effectiveness of IACs in chronic asthma management. Therefore when coupling current findings with recent efficacy evidence, more evidence is clearly needed on IAC safety in asthma patients before their use in asthma management.

Importantly, the TALC study focused on tiotropium and not ipratropium, which was the predominant IAC in this analysis. There was limited sample size with respect to patients exposed to tiotropium. Nevertheless, these results raise important questions about the

cardiovascular safety profile of anticholinergics in patients with asthma.

Further evidence of the drug effect is provided by the results from the analysis excluding patients with comorbid heart disease. These patients are at a higher risk for arrhythmia. In fact, the proportion of patients with comorbid heart disease was higher in the cases (1.13%) compared with controls (0.08%). However, after excluding those with comorbid heart conditions, active exposure to IACs was still associated with a 52% increased risk for arrhythmia.

Several limitations to our study need to be considered when interpreting the results. First, exposure was defined based on prescription fills recorded in administrative data, which may not be indicative of actual drug use. Active users of anticholinergics were classified into low- and high-dose groups based on the quantity dispensed. Hence patients were possibly misclassified if they were not taking the medication as dispensed. However, it is not likely that this misclassification was different between cases and controls.

Second, the outcome of arrhythmic events was defined based on a wide range of ICD-9 codes placed anywhere in the medical claim. Although inclusion of ICD-9 codes such as 785 (palpitations) could potentially be secondary to arrhythmia, we thought it was important to detect any signal of cardiovascular events in a population of children, adolescents, and young adults.

Third, there was no information on frequency of symptoms to determine asthma severity, a potential confounder in the association between IACs and arrhythmia. Exacerbations of asthma carry a theoretical arrhythmogenic risk due to multiple pathophysiologic events such as hypoxia, hypercapnia, and elevated intrathoracic pressures, which in turn have an effect on cardiac blood return.^{30–32} However, proxy measures for asthma exacerbations such as asthma-related emergency department visits, SABA canisters dispensed, and number of acute exacerbations in the 180 days before the event date were adjusted for in the analysis.

Conclusion

In this analysis, the use of inhaled ipratropium was associated with an increased risk of arrhythmia in adolescents and young adults with asthma compared to non-users. Patients 12–24 years of age and those prescribed ipratropium were at an increased risk for arrhythmia. It

should be noted that the absolute risk was low. Nevertheless, health care providers are advised to be cautious before incorporating anticholinergics into the chronic management of asthma. This risk may also be important to consider in other populations where predisposition to arrhythmia is increased. Further research on IAC therapy in chronic asthma management is needed to understand the potential risks more fully.

Acknowledgment

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References

1. Kelly HW, Sorkness CA. Chapter 33. Asthma. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey ML, eds. *Pharmacotherapy: a pathophysiologic approach*, 8th ed. New York: McGraw-Hill, 2011;439–470.
2. Rang H, Dale M, Ritter J, Flower R. Pulmonary disease and its treatment. In: Rang H, Dale M, Ritter J, Flower R, eds. *Pharmacology*, 6th ed. New York, NY: Churchill Livingstone, 2007;357–367.
3. Sears MR. The addition of long-acting beta-agonists to inhaled corticosteroids in asthma. *Curr Opin Pulm Med* 2011; 17:23–8.
4. Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. *Cochrane Database Syst Rev*. 2009; CD007949.
5. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1481–8.
6. Westby MJ, Benson M, Gibson PG. Anticholinergic agents for chronic asthma in adults. *Cochrane Database Syst Rev* 2004; CD003269.
7. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006;130:1695.
8. Sanoski CA, Dekker Schoen M, Bauman JL. The arrhythmias. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey ML, eds. *Pharmacotherapy: a pathophysiologic approach*, 7th ed. New York: McGraw-Hill, 2008;279–314.
9. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the lung health study. *Am J Respir Crit Care Med* 2002;166:333.
10. Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006;61:854–862.
11. Guite HF, Dundas R, Burney PGJ. Risk factors for death from asthma, chronic obstructive pulmonary disease, and cardiovascular disease after a hospital admission for asthma. *Thorax* 1999;54:301–7.
12. Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008;149:380.
13. Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137:13.

14. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008;300:1439.
15. Hilleman DE, Malesker MA, Morrow LE, Schuller D. A systematic review of the cardiovascular risk of inhaled anticholinergics in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2009;4:253–63.
16. Tamariz L, Harkins T, Nair V. Mini-sentinel systematic evaluation of health outcome of interest definitions for studies using administrative data: cardiac arrhythmias report. Miami, FL: Humana; January 25, 2011.
17. Lubin JH, Gail MH. Biased selection of controls for case-control analyses of cohort studies. *Biometrics* 1984;40:63–75.
18. Robins JM, Gail MH, Lubin JH. More on “Biased selection of controls for case-control analyses of cohort studies.” *Biometrics* 1986;42:293–9.
19. Ganz LI. Epidemiology of and risk factors for atrial fibrillation. In: Basow DS, ed. *UpToDate*. Waltham, MA: UpToDate, 2011.
20. Klein I. Cardiovascular effects of hyperthyroidism. In: Basow DS, ed. *UpToDate*. Waltham, MA: UpToDate, 2011.
21. Wilson PW. Overview of the risk factors for cardiovascular disease. In: Basow DS, ed. *UpToDate*. Waltham, MA: UpToDate, 2011.
22. De Ponti F, Poluzzi E, Cavalli A, Recanatini M, Montanaro N. Safety of non- antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. *Drug Saf* 2002;25:263–86.
23. Haverkamp W, Breithardt G, Camm JA. The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications report on a policy conference of the European Society of Cardiology. *Cardiovasc Res* 2000;47:219–33.
24. Schatz M, Nakahiro R, Jones CH, Roth RM, Joshua A, Petitti D. Asthma population management: development and validation of a practical 3-level risk stratification scheme. *Am J Manag Care* 2004;10:25–32.
25. Schatz M, Zeiger R, Yang S-JT, et al. Relationship of asthma control to asthma exacerbations using surrogate markers within a managed care database. *Am J Manag Care* 2010;16:327–33.
26. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989;79:340–9.
27. Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;162:75–80.
28. Palmer CN, Lipworth BJ, Lee S, Ismail T, Macgregor DF, Mukhopadhyay S. Arginine-16 beta2 adrenoceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. *Thorax* Nov 2006;61:940–4.
29. Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. *Thorax* 2000;55:762–7.
30. Levine PA, Klein MD. Mechanisms of arrhythmias in chronic obstructive lung disease. *Geriatrics* 1976;31:47–56.
31. Maguire JF, O'Rourke PP, Colan SD, Geha RS, Crone R. Cardiotoxicity during treatment of severe childhood asthma. *Pediatrics* 1991;88:1180–6.
32. Tirlapur VG, Mir MA. Nocturnal hypoxemia and associated electrocardiographic changes in patients with chronic obstructive airways disease. *N Engl J Med* 1982;306:125–30.