Inhaled Beta-2 Adrenergic Receptor Agonists and Primary Cardiac Arrest

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PURPOSE: We sought to investigate if short-acting, inhaled β_2-adrenergic receptor agonists were associated with higher risk of primary cardiac arrest in patients with asthma or chronic obstructive pulmonary disease (COPD).

SUBJECTS AND METHODS: We conducted a population-based study involving 454 patients enrolled in a health maintenance organization, aged 40 to 79 years, who had asthma or COPD and who experienced primary cardiac arrest during 1980 to 1994. We randomly selected 586 controls from strata of enrollees, defined by age, sex, calendar year, and prior heart disease. Medication use was assessed from computerized pharmacy data, and risk factors from medical record review.

RESULTS: Use of inhaled β-agonists was associated with a twofold increased risk of primary cardiac arrest (odds ratio [OR] = 1.9; 95% confidence interval [CI]: 1.1 to 3.3) among patients with asthma, but not among those with COPD (OR = 1.3; 95% CI: 0.6 to 2.7), after adjustment for risk factors. This association was observed only with use of two or more canisters of metered-dose, inhaled β-agonists for 3 months, and when inhaled steroids were not used.

CONCLUSION: These results support current guidelines recommending inhaled steroids as first-line asthma therapy. **Am J Med. 2002;113:711–716.** ©2002 by Excerpta Medica Inc.

Short-acting, inhaled β_2-adrenergic receptor agonists (β-agonists) are used to treat acute bronchospasm and to prevent exercise-induced bronchospasm in patients with asthma or chronic obstructive pulmonary disease (COPD) (1,2). However, there is concern about their safety because they increase heart rate, prolong the electrical action potential duration, and may cause hypokalemia (3–5), factors that increase the risk of sudden cardiac death (6–12). In contrast, β_2-adrenergic receptor antagonists (beta-blockers) decrease the risk of sudden cardiac death (13).

Use of inhaled β-agonists is associated with an increased risk of asthma death in a dose-response fashion (14). Because severe asthma symptoms lead to higher use of inhaled β-agonists (2), asthma severity might explain the association of inhaled β-agonists with asthma death (15,16). In the Saskatchewan Asthma Epidemiologic Project, the oral and nebulized formulations, but not the metered-dose inhaled form, were also associated with an increased risk of sudden cardiac death (17). However, there were few sudden cardiac deaths in that study, and information on risk factors such as smoking was not available.

We sought to investigate the association between the use of short-acting, inhaled β-agonists and the risk of incident primary cardiac arrest in a population-based case-control study that combined assessment of exposure to inhaled β-agonists with information on risk factors, morbidity, and other drug therapies.

METHODS

Study Design and Sample

Data were originally collected for a population-based case-control study of the relation between medications and the risk of primary cardiac arrest among enrollees of Group Health Cooperative, a large health maintenance organization in western Washington State. The present study was restricted to enrollees (cases and controls), who had a history of asthma or COPD. Diagnosis was based on either a physician diagnosis noted in the health plan medical record or prescription of a β-agonist. Eligible subjects could not have had metastatic cancer, brain tumor, end-stage liver disease, or respiratory failure.

Cases (n = 586) were 40 to 79 years of age and had incident, out-of-hospital primary cardiac arrest between January 1, 1980, and December 31, 1994. Primary cardiac arrest was defined as a sudden pulseless condition in the absence of evidence that a noncardiac condition was the cause of the cardiac arrest. We identified the cases from

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Emergency Medical Services databases and from Group Health Cooperative databases. Deaths that could not be confirmed to be of cardiac origin, and all deaths that might have been due to asthma, were excluded.

Controls were a random sample of Group Health Cooperative enrollees (n = 722), stratified by calendar year, age (decade), sex, and treatment with digoxin or nitroglycerin, a marker of prior heart disease. Use of digoxin or nitroglycerin served as a proxy for heart disease in the sampling of controls, as this information was available on all enrollees through automated pharmacy records. The ratio of controls to cases was approximately 2 to 1 in the original case-control study.

We also excluded 36 cases and 23 controls who were enrolled for less than 2 years because we needed 2 years of exposure information, 67 cases and 95 controls who used beta-blockers, 4 cases and 5 controls who used oral β-agonists, 6 cases and 2 controls who had pulmonary disease other than asthma or COPD, and 19 cases and 11 controls who could not be matched. The remaining sample included 454 cases and 586 controls.

Data Collection

We reviewed the ambulatory medical record to identify comorbid conditions, to determine eligibility, and to collect information on key covariates. We used the organization's computerized pharmacy database to assess use of inhaled β-agonists and other medications, including inhaled and oral steroids, theophylline, and ipratropium, from prescriptions filled up to 2 years before the index date. The index date was the date of primary cardiac arrest for cases, and for controls, a randomly assigned date within the same calendar year that they were sampled.

Statistical Analysis

Analyses were performed using Stata 7.0 (Stata Corporation, College Station, Texas). In descriptive analyses, the prevalence of risk factors was compared between cases and controls, and between users and nonusers of inhaled β-agonists in the control group, using chi-squared tests for categorical variables and *t* tests for continuous variables. We used conditional logistic regression to obtain estimates of the relative risk (odds ratio) of primary cardiac arrest associated with an inhaled β-agonist, accounting for age decade, sex, calendar year, and use of digoxin or nitroglycerin, and adjusting for age, history of heart disease, and key covariates. Covariates included hypertension, heart failure, stroke, smoking, myocardial infarction, angina, diabetes, depression, peripheral vascular disease, heavy alcohol use, use of antiarrhythmic medications, total number of visits to a physician in the year before the index date, performance of a pulmonary function test (as a marker of respiratory disease severity), electrocardiography (as a marker of subclinical heart disease), use of inhaled or oral steroids, and use of theophylline or ipratropium. They were retained in the final model if there was a notable effect on the odds ratios associated with β-agonist use.

In initial analyses, we computed odds ratios and 95% confidence intervals associated with the use of inhaled β-agonists in the 3-month window before the index date, compared with no use during that period. In further analyses, we defined mutually exclusive categories of use of inhaled β-agonists, with nonusers of β-agonists in the prior 2 years as the reference group.

RESULTS

We identified 454 eligible patients who had primary cardiac arrest and 586 controls who had a history of asthma or COPD. Coronary heart disease, cardiovascular disease, and risk factors such as diabetes and smoking were more prevalent among cases than controls (Table 1). The relatively high prevalence of both coronary heart disease and asthma among controls was due to the stratified sampling of control patients and the restriction of both cases and controls to patients with asthma or COPD. Coronary heart disease and current smoking were more common among patients with COPD than among those with asthma; however, the case-control differences in risk factor prevalence were similar between the two groups of patients.

When we assessed use of inhaled β-agonists from prescriptions filled during the 3-month window before the index date, we found that 26% of cases (118/454) and 20% of controls (116/586) received metered-dose, inhaled β-agonists (Table 1). Seventy-one percent (167/234) used albuterol, 24% (n = 57) used metaproterenol, 7% (n = 17) used terbutaline, and 2% (n = 4) used isoproterenol. The relative use of β-agonist subtypes was similar in cases and controls. Patients with asthma were more likely than those with COPD to have received inhaled β-agonists (47% of cases [67/142] and 30% of controls [74/244]).

Recent use of inhaled β-agonists was also associated with male sex, a history of stroke, unstable angina, asthma, and, possibly, hypertension and current smoking (Table 2).

Use of inhaled β-agonists in the 3-month window before the index date was associated with a higher risk of primary cardiac arrest (odds ratio [OR] = 1.8; 95% confidence interval [CI]: 1.2 to 2.6), after adjustment for age, sex, calendar year, history of heart disease, use of digoxin or nitroglycerin, hypertension, heart failure, current smoking, stroke, use of inhaled steroids, and use of oral steroids. The association was observed in both those with heart disease (OR = 1.7; 95% CI: 1.1 to 2.6) and those without clinically diagnosed heart disease (OR = 2.3; 95% CI: 1.1 to 5.0; *P* for interaction = 0.57). Use of inhaled β-agonists was associated with an increased risk of

Table 1. Characteristics of Cases and Controls

Characteristic	All Patients*		Patients with Asthma		Patients with Chronic Obstructive Pulmonary Disease	
	Cases (n = 454)	Controls (n = 586)	Cases (n = 142)	Controls (n = 244)	Cases (n = 263)	Controls (n = 273)
	Number (%) or Mean ± SD					
Male sex	331 (73)	413 (71)	96 (68)	151 (62)	208 (79)	229 (84)
Age (years)	70 ± 8	69 ± 8	69 ± 8	67 ± 9	71 ± 7	70 ± 6
Asthma	142 (31)	244 (42)	(100)	(100)	(0)	(0)
Chronic obstructive pulmonary disease	354 (78)	396 (68)	91 (64)	123 (50)	(100)	(100)
Clinically diagnosed heart disease	329 (72)	392 (67)	101 (71)	156 (64)	194 (74)	196 (72)
Myocardial infarction	161 (35)	108 (18)	41 (29)	34 (14)	103 (39)	65 (24)
Unstable angina	18 (4)	10 (2)	8 (6)	4 (2)	9 (3)	3 (1)
Heart failure	213 (47)	121 (21)	54 (38)	36 (15)	133 (51)	74 (27)
Stroke	49 (11)	24 (4)	17 (12)	5 (2)	29 (11)	17 (6)
Peripheral vascular disease	133 (29)	98 (17)	33 (23)	35 (14)	90 (34)	57 (21)
Hypertension	215 (47)	209 (36)	58 (41)	87 (36)	128 (49)	102 (37)
Diabetes mellitus	73 (16)	46 (8)	23 (16)	23 (9)	41 (16)	19 (7)
Depression	95 (21)	113 (19)	32 (23)	44 (18)	56 (21)	50 (18)
Current smoking	182 (40)	166 (28)	32 (23)	37 (15)	141 (54)	118 (43)
Heavy alcohol use	79 (17)	47 (8)	17 (12)	9 (4)	61 (23)	32 (12)
Use of inhaled β-agonists during 3 months before index date	118 (26)	116 (20)	67 (47)	74 (30)	33 (13)	27 (10)
Use of inhaled steroids during 3 months before index date	44 (10)	62 (11)	33 (23)	48 (20)	9 (3)	12 (4)

* Includes patients with unknown indications.

primary cardiac arrest among patients with asthma (OR = 1.9; 95% CI: 1.1 to 3.3), but not among patients with COPD (OR = 1.3; 95% CI: 0.6 to 2.7).

The association between use of inhaled β-agonists and primary cardiac arrest was similar regardless of whether one or more metered-dose canisters were used (Table 3). However, among patients with asthma, a positive association was observed with increased use of inhaled β-agonists. Compared with no use in the 2 years before the index date, use of one canister of inhaled β-agonist in the

Table 2. Prevalence of Risk Factors among Controls Who Used or Did Not Use Inhaled Beta-Agonists in the 3 Months before the Index Date

Risk Factor	Nonusers (n = 470)	Used Inhaled β-Agonists (n = 116)	*P* Value
	Number (%) or Mean ± SD		
Male sex	344 (73)	69 (59)	0.004
Age (years)	69 ± 8	69 ± 8	0.51
Asthma	170 (36)	74 (64)	0.001
Chronic obstructive pulmonary disease	315 (67)	81 (70)	0.56
Clinically diagnosed heart disease	310 (66)	82 (71)	0.33
Myocardial infarction	21 (19)	87 (19)	0.92
Unstable angina	4 (1)	6 (5)	0.001
Heart failure	96 (20)	25 (22)	0.79
Stroke	23 (5)	1 (1)	0.05
Peripheral vascular disease	82 (17)	16 (14)	0.35
Hypertension	159 (34)	50 (43)	0.06
Diabetes mellitus	37 (8)	9 (8)	0.97
Depression	84 (18)	29 (25)	0.08
Current smoking	146 (31)	20 (17)	0.003
Heavy alcohol use	39 (8)	8 (7)	0.62

Table 3. Association between Use of Metered-Dose, Inhaled Beta-Agonists and the Risk of Primary Cardiac Arrest

	All Patients		
	Cases (n = 454)	Controls (n = 586)	Odds Ratio (95% Confidence Interval)*
Use of inhaled β-agonists	Number		
No use in past 2 years	258	332	1.0
Number of metered-dose canister in past 3 months			
0	68	135	0.6 (0.4–0.9)
1	39	38	1.5 (0.9–2.6)
2 or more	67	71	1.5 (0.9–2.5)
Use of nebulizers in past 3 months	22	10	2.7 (1.1–6.6)
	Patients with Asthma		
Use of inhaled β-agonists	Cases (n = 142)	Controls (n = 244)	
	Number		
No use in past 2 years	41	108	1.0
Number of metered-dose canister in past 3 months			
0	26	61	0.8 (0.4–1.7)
1	10	16	1.2 (0.4–3.5)
2 or more	46	52	2.0 (0.9–4.2)
Use of nebulizers in past 3 months	19	7	5.3 (1.6–17.8)
	Patients with COPD		
Use of inhaled β-agonists	Cases (n = 263)	Controls (n = 273)	
	Number		
No use in past 2 years	207	208	1.0
Number of metered-dose canister in past 3 months			
0	21	36	0.5 (0.3–1.0)
1	13	8	1.9 (0.6–6.0)
2 or more	19	18	0.8 (0.3–2.1)
Use of nebulizers in past 3 months	3	3	1.3 (0.2–8.3)

* Adjusted for age, sex, calendar year, use of digoxin or nitroglycerin, history of heart disease, hypertension, heart failure, stroke, current smoking, use of inhaled steroids, and use of oral steroids.

COPD = chronic obstructive pulmonary disease.

previous 3 months was associated with a 1.2-fold increase in the risk of primary cardiac arrest, whereas use of two or more canisters was associated with a twofold increased risk. Nebulized β-agonists were associated with the highest risk of primary cardiac arrest (Table 3). However, there was no evidence of a dose response among patients with a history of COPD (Table 3).

Of the patients with asthma who received two or more canisters of inhaled β-agonists, 70% of cases (32/46) and 64% of controls (33/52) also received a prescription for theophylline, and 17% of cases (8/46) and 10% of controls (5/46) were prescribed ipratropium. However, the association between the use of two or more canisters of inhaled β-agonists and primary cardiac arrest changed only slightly upon further adjustment for theophylline (OR = 2.1; 95% CI: 0.9 to 4.5) or ipratropium (OR = 1.9; 95% CI: 0.9 to 4.0).

Inhaled steroids were used largely as second-line therapy, in combination with inhaled or nebulized β-agonists. Among patients who received two or more canisters of inhaled β-agonists, 25% (17/67) of cases and 52% (37/71) of controls also used inhaled steroids. When inhaled steroids were added to the treatment regimen, the use of inhaled β-agonists was not associated with risk of pri-

Table 4. Association between Metered-Dose, Inhaled Beta-Agonists and the Risk of Primary Cardiac Arrest, by Use of Inhaled Steroids

	All Patients		
	Cases (n = 454)	Controls (n = 586)	Odds Ratio (95% Confidence Interval)*
Use of inhaled β-agonists in past 3 months:	Number		
No use in past 2 years	258	332	1.0
Number of metered-dose canister in past 3 months			
0	68	135	0.6 (0.4–0.9)
1	39	38	1.4 (0.8–2.5)
2 (without inhaled steroids)	50	34	1.9 (1.1–3.3)
2 (with inhaled steroids)	17	37	0.54 (0.3–1.1)
Use of nebulizers in past 3 months	22	10	2.2 (0.9–5.2)
	Patients with Asthma		
	Cases (n = 142)	Controls (n = 244)	
Use of inhaled β-agonists in past 3 months	Number		
No use in past 2 years	41	108	1.0
Number of metered-dose canister in past 3 months			
0	26	61	0.8 (0.4–1.6)
1	10	16	1.1 (0.4–3.3)
2 (without inhaled steroids)	33	22	2.5 (1.1–5.4)
2 (with inhaled steroids)	13	37	0.6 (0.2–1.6)
Use of nebulizers in past 3 months	19	7	3.8 (1.1–12.3)

* Adjusted for age, sex, calendar year, use of digoxin or nitroglycerin, history of heart disease, hypertension, heart failure, stroke, current smoking, and use of oral steroids.

mary cardiac arrest, whereas when steroids were not included, the use of two or more canisters of inhaled β-agonists was associated with a twofold increase in the risk of primary cardiac arrest (Table 4).

DISCUSSION

We observed that high use of metered-dose, inhaled β-agonists was associated with a twofold increase in the risk of primary cardiac arrest among patients with asthma when inhaled steroids were not used. Use of a β-agonist in nebulizers was also associated with higher risk.

The National Asthma Education and Prevention Program (1) recommends using inhaled steroids as first-line therapy for asthma and using inhaled β-agonists sparingly, because inhaled steroids have been shown to be safe (18) and because decreasing the need for inhaled β-agonists minimizes possible adverse effects. Because inhaled steroids were used as second-line agents during our study (which took place between 1980 and 1994), we could not compare inhaled β-agonists with inhaled steroids as first-line therapy. Nevertheless, our results support the current recommendations.

Inhaled steroids may have affected drug use, disease, or both. They may have reduced the need for metered-dose, inhaled β-agonists by controlling asthma symptoms (2), thereby reducing possible adverse drug effects. Decreased asthma severity due to inhaled steroid use may also have led to the decreased risk of primary cardiac arrest (19). Although we accounted for several markers of asthma severity in our analyses, we cannot distinguish between these possibilities.

We observed a weak, statistically nonsignificant association between inhaled β-agonists and primary cardiac arrest, with no evidence of a dose response, among patients with COPD. Prevalence of asthma drug use among patients with COPD was low, and the lack of association may be due to chance. Alternatively, the risks and benefits of inhaled β-agonists may have differed among patients with COPD. Inhaled β-agonists might decrease the severity of COPD, which was a risk factor for primary cardiac arrest in our study, thereby mitigating possible adverse effects. It is also possible that COPD increases the background risk of primary cardiac arrest, and inhaled β-agonists do not increase the risk further.

In a report from the Saskatchewan Asthma Epidemiologic Project on the association of β-agonists with sudden cardiac death among patients with asthma (17), the risk of sudden cardiac death increased among patients who had been dispensed oral or nebulized β-agonist (relative

risk [RR] = 2.4; 95% CI: 1.0 to 5.4), but use of inhaled β-agonists did not significantly increase the risk of sudden cardiac death (RR = 1.2; 95% CI: 0.5 to 2.7). We observed an association of both nebulized and inhaled β-agonists with a higher risk of primary cardiac arrest. However, there were only 30 sudden deaths in the Saskatchewan cohort, and information was not available for several known risk factors, including hypertension, diabetes, diagnoses of cardiovascular diseases, and smoking, which could have confounded the association of β-agonist use with sudden cardiac death. Alternatively, different characteristics of metered-dose, inhaled β-agonist use (dose, combined use with inhaled steroids) may explain the difference in results.

Our study has several limitations. Recent exposure was defined on the basis of prescriptions filled in the 3 months before the index date. Because short-acting β-agonists are used as needed, we do not know when subjects actually used them. There may also have been confounding by severity of asthma. We minimized this possibility by adjusting for markers of severity of respiratory diseases, such as performance of a pulmonary test function, use of ipratropium, and use of oral steroids. Lastly, the observational design may have led to residual confounding by unmeasured factors or incompletely measured risk factors.

The strengths of our study include the population-based design, objective assessment of exposure to β-agonists, and extensive assessment of potential confounding factors. We addressed the possibility of confounding by matching, multivariate adjustments, and restriction.

In conclusion, our results suggest that in patients with asthma, an increased risk of primary cardiac arrest is associated with high use of metered-dose, inhaled β-agonists, as well as with use of nebulized β-agonists. Inhaled steroids may lower the risk of cardiac arrest by decreasing the need for inhaled β-agonists and by enhancing efficacy of the treatment of the underlying pulmonary condition (19,20). Although these findings need to be confirmed, our results support current recommendations (1) to use inhaled steroids as first-line agents in the treatment of asthma.

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