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Long-Acting Beta-Agonists And The Risk of Intensive Care Unit Admission in Children

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Abstract

Objective—A possible association between long-acting beta-agonists (LABA) and severe asthma exacerbations including death remains controversial. We examined whether LABA in the setting of combination therapy with inhaled corticosteroids (ICS) increases the risk of near-fatal asthma in children using a case-control study design.

Methods—Medical records from admissions for asthma exacerbations in children 4 to 18 years of age during the 2005 calendar year at Children's Hospital of Pittsburgh of UPMC were reviewed. Cases and controls were determined by pediatric intensive care (PICU) and floor admission, respectively. Exposure was defined by LABA use in combination with ICS versus ICS alone.

Results—Records from 156 PICU and 207 pediatric floor admissions were reviewed. Records were excluded for non-asthma admissions, complicated pneumonias, debilitating comorbid disorders and multiple admissions leaving 85 PICU and 96 floor admissions. LABA use in combination with ICS did not increase the risk of PICU admission (OR 1.07, 95% CI 0.46–2.52), compared to ICS only without LABA. After adjusting for demographics, asthma severity, history of PICU admissions and concurrent infection, LABA/ICS use still did not increase the risk of PICU admission (aOR 0.84, 95% CI 0.26–2.76), compared to ICS alone. There were no deaths and five intubations within the study period.

Conclusions—The combination of LABA and ICS did not appear to increase the risk of near-fatal asthma in children.

Keywords

Asthma; Long-acting Beta-agonist; Inhaled Corticosteroids; Drug Safety

Introduction

Long-acting beta-agonists (LABA) are frequently prescribed for both pediatric and adult patients with moderate to severe persistent asthma. Randomized controlled trials suggest that LABA increase the risk of asthma-related mortality. Due to these findings, the United States Food and Drug Administration (FDA) mandated "black-box" warning labels for

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products containing salmeterol or formoterol, as LABA "may increase the chance of severe asthma episodes and death." The US FDA recommends that LABA should be used only in conjunction with inhaled corticosteroids (ICS) and for the shortest possible time.[1]

The Serevent National Surveillance study (SNS) showed a non-statistically significant three-fold increase in the risk of death associated with salmeterol (12 asthma-related deaths in 16,787 patients receiving 16 weeks of LABA treatment, compared to 2 deaths in 8,393 control patients).[2] Similarly, the Salmeterol Multicenter Asthma Research Trial (SMART) demonstrated salmeterol use (over 28 weeks) was associated with increased respiratory-related death (RR 2.2, 95% CI 1.1–4.4), asthma-related death (RR 4.4, 95% CI 1.2–15.3), and combined asthma-related death or life-threatening exacerbation (RR 1.7, 95% CI 1.0–2.9).[3] Neither SNS nor SMART was designed to evaluate the safety of LABA used in conjunction with ICS.[4,5]

Whether concomitant use of ICS prevent or mitigate the risks associated with LABA is controversial.[6–10] In adults, meta-analyses of combined LABA/ICS use show that the risk of exacerbations (mainly hospitalizations) as neutral or reduced, and do not demonstrate increased mortality.[11–14] In an FDA meta-analysis involving 110 trials and 60,954 patients, Levenson reported the mortality risk difference (MRD) of LABA stratified by mandatory ICS use.[15] For patients receiving LABA only, the MRD was 3.63 (95% CI 1.51–5.75) in 1000 patients, while among patients receiving LABA and ICS combined, the MRD was non-significant (0.25, 95% CI−1.69−2.18). Levenson reported no deaths or intubations associated with single-device LABA/ICS combinations.[15]

There is a paucity of studies examining LABA safety in children. An early review, noted an apparent 3–21 fold increased risk of hospitalizations in children treated with LABA in addtion to ICS,[16] although the way in which studies were chosen for inclusion in this analysis has been criticised.[17] One AstraZeneca-sponsored review studied formoterol use in 41 trials and 11,849 children and adolescents under the age of 18 years, 82% of whom used concomitant ICS. There was one death among 7,796 formoterol-treated patients, and none among 4,053 non-LABA-treated patients, and no difference in the frequency of asthma-related hospitalizations in either children or adolescents.[18] Another metanalysis showed an increased risk of hospitalization in children compared to adults (RR 3.9 versus 2.0) but included studies in which patients were not on ICS.[8] Very recently, a detailed meta-analsys from McMahon et al. examined the composite endpoint of death, intubation and asthma-related hospitalization.[19] While a substantially increased risk fo this endpoint was found for LABA use overall, there was no difference in patients who recieved concomitant ICS (in addition to LABA) as part of the relevant trial.[19]

We used pediatric intensive care unit (PICU) admissions as a correlate of life-threatening asthma exacerbations, and examined whether LABA use in conjunction with ICS increases the likelihood of PICU admission using a case-control study design.

Methods

Study design

We developed a case-control study to examine the odds of PICU admission as a correlate of life-threatening asthma exacerbation with LABA use in combination with ICS versus ICS alone. Records of patients age 4 to 18 years admitted to the pediatric medical floor (PMF) and the PICU at Children's Hospital of Pittsburgh of UPMC with diagnoses of asthma (ICD 493.*) or wheezing (ICD 786.07) during 2005 were examined. The protocol for this study was approved by the University of Pittsburgh Institutional Review Board.

Cases and Controls

Cases were determined by severe asthma exacerbations requiring PICU admission. Controls were defined by asthma exacerbations requiring PMF admission. Indications for PICU admission for asthma exacerbation were well-defined by a clinical practice guideline is use at Children's Hospital of Pittsburg of UPMC during the period covered by this study. These included requiring (or imminently requiring) any therapy beyond albuterol treatment every 2 hours (including, but not limited to, continuous albuterol, heliox administration, high flow nasal cannula, magnesium, aminophylline, positive airway pressure CPAP or BiPAP, and intubation and mechanical ventilation).

In the primary analysis, exposure was defined by (home medication) LABA use in combination with ICS versus ICS alone at baseline. In a secondary analysis, exposure was defined by no controller medication (albuterol use alone) versus ICS alone at baseline.

Inclusions and Exclusions

Admissions that resulted from indications other than acute asthma exacerbation were excluded as were PICU admissions that resulted solely from diastolic hypotension due to albuterol use. In cases of multiple PICU or PMF admissions for a given patient, only the most recent admission was included. For both PICU and PMF admissions, the following conditions led to exclusion: underlying chronic pulmonary conditions other than asthma, underlying chronic debilitating conditions, complicated pneumonias including lung abscesses, empyemas, effusions requiring intervention, and sepsis.

Demographic Variables and Asthma Admissions

Demographic variables collected included age, sex, self-reported race, and insurance status. Medical history variables collected included history of asthma and other significant past medical history. Variables collected relating to index exacerbation included reported symptoms of upper or lower respiratory infection, chest x-ray findings, antibiotics and corticosteroid administration.

Asthma Triggers and Atopic Comorbidities

Variables collected related to asthma triggers and atopic comorbidities included upper or lower respiratory infections, weather conditions, pet ownership or exposure, second-hand smoke exposure, allergic rhinitis, atopic dermatitis and food allergies. Family history variables collected included asthma and atopy. Socioeconomic risk factors collected included history of subspecialty asthma care, and poor medication adherence.

Admission Outcomes

Outcome variables collected included length of stay, positive airway pressure, intubation and death. Exposure variables collected included no controller medication (albuterol alone), ICS, ICS dose (low, medium or high), LABA, leukotriene modifiers, cromolyn or nedocromil, theophylline and recent oral corticosteroids. ICS dose was categorized using the table of estimated comparative daily dosages of inhaled corticosteroids from the NAEPP Expert Panel Report 3 Guidelines for the Diagnosis and Management of Asthma.[20]

Asthma Severity

Variables collected relating to asthma severity classification included frequency of day-time symptoms, frequency of night-time symptoms, and documented severity classification (intermittent, mild persistent, moderate persistent and severe persistent). To mitigate the effects of missing values, a combined asthma severity classification variable was created (intermittent, mild persistent and moderate-severe persistent) by preferentially using

documented severity classification, then ICS-dose estimated severity classification. Other variables collected relating to asthma severity included history of prior ICU and floor admission and prior intubation for asthma.

Statistical analysis

Data were analyzed using Stata SE 9.2 for Windows (College Station, Texas). Unadjusted odds ratios (OR) and adjusted odds ratios (aOR) were calculated using binary logistic regression models. P-values were calculated using chi-square tests and Fisher's exact tests (for rare events).

Candidate variables for inclusion in the logistic regression models as predictor variables were selected based on previously identified clinical importance. Significant covariates and interaction variables were selected for inclusion in the final models if they produced a ten-percent difference in the effect size (adjusted odds ratio) for the primary exposure-outcome association (LABA-PICU), and if the confounding relationship was clinically plausible.

Stratification analysis was performed to examine odds of PICU admission with LABA/ICS use compared to ICS alone for various asthma severity classifications (intermittent, mild persistent or moderate-severe persistent), based on a combination of documentation and estimate from ICS dose. Odds ratios were estimated using logistic regression and exact logistic regression (for small sample sizes) limited to each subset.

SAS Proc Power was used to determine the sample size required to achieve 80% power (assuming 5% type I error) to detect a difference in the probability of ICU versus floor admission using logistic regression in patients using ICS/LABA compared to ICS alone. The sample sizes necessary to detect a two, three, or four-fold odds ratio of PICU to PMF admission were 277, 113 and 73, respectively.

Results

Baseline demographic and socioeconomic characteristics

Records from 156 PICU and 207 PMF admissions were reviewed. Records were excluded for non-asthma admissions, complicated pneumonias, debilitating comorbid disorders and multiple admissions (only most recent admission was studied), leaving 85 PICU and 96 floor admissions (n = 181).

There were no significant demographic differences between PICU and PMF groups in terms of age, gender, race, access to subspecialty care, insurance status, or concerns with medical compliance (Table 1). The mean age was 9 years in the PICU group, and 8 years in the PMF group. Girls represented 52% of the PICU group, compared to 39% of the PMF group. There were 37% self-reported non-Hispanic blacks in the PICU group, and 43% in the PMF group.

Baseline asthma history, severity and risk factors

There were no significant differences between PICU and PMF groups in history of asthma, asthma severity, home medications, comorbid atopic disorder and environmental risk factors, except for history of ICU admission, which was increased in the PICU patients (Table 2). In both groups, patients were primarily classified as having intermittent or moderate to severe persistent asthma. Patients without a history of asthma were classified as intermittent. There was a significantly greater proportion of prior ICU admission in the PICU group, in comparison to the control group ($p = 0.006$). There were 7 children with a history of intubation in the PICU group, compared to 2 in the PMF group.

Asthma exacerbation characteristics and outcomes

Patients admitted to the PICU had a significantly greater proportion of abnormal chest x-ray findings including hyperinflation (17% versus 5%) and atelectasis (19% versus 7%), and of treatment with antibiotics for coverage of atypical organisms (48% versus 27%) and typical pneumonia (35% versus 19%), compared to control (Table 3). The PMF group had a significantly greater proportion of patients reporting symptoms of upper or lower respiratory infection ($p = 0.008$). All patients received either oral or intravenous corticosteroids during their hospitalization. There were no deaths in the study period (Table 4). There were 5 intubations in the study period; 2 in the LABA/ICS group, and 3 in the no controller medication group ($p = 0.447$). There were 3 patients who received positive airway pressure (CPAP or BiPAP); 1 in the LABA/ICS group, and 2 in the ICS only group ($p = 0.139$).

Logistic regression analysis for the likelihood of PICU admission

Covariates included in the final logistic regression model were age, sex, race, history of ICU admissions, respiratory infection, and either severity based on a combination of documentation and estimate from ICS dose, or severity based on documentation only.

LABA use in combination with ICS did not increase the likelihood of PICU admission (OR 1.07, 95% CI 0.46–2.52), compared to ICS only (Table 5). After adjusting for demographics, asthma severity (based on a combination of documentation and estimate from ICS dose), history of ICU admissions and concurrent infection, LABA/ICS use still did not increase the risk of PICU admission (aOR 0.82, 95% CI 0.25–2.73). Using a similar analysis, but with the covariate of asthma severity limited to documentation only, LABA/ICS similarly did not increase the likelihood of PICU admission (aOR 0.35, 95% CI 0.07–1.79).

Being on no controller medication did not significantly increase the likelihood of PICU admission in either the crude analysis (OR 1.40, 95% CI 0.67–2.97) or adjusted analysis (aOR 2.15, 95% CI 0.67–6.87), utilizing the same covariates.

Finally, we examined the risk of PICU admission for patients taking LABA/ICS versus ICS alone using stratification analysis by asthma severity. There were no substantial difference between patients in each category of asthma severity (intermittent, mild persistent and moderate-severe persistent) although the numbers in each strata were small (data not shown).

DISCUSSION

In this study, we examined the likelihood of life-threatening pediatric asthma exacerbations in the setting of LABA and ICS combination therapy using a retrospective case-control study design. Because the incidence of asthma-related death is low, we used asthma-related PICU admission as a surrogate clinical outcome.[21] Admission to the PICU versus medical floor was based on well-defined criteria prescribed by a clinical practice guideline in use during the study period. Patients requiring acute therapy more intensive than inhaled albuterol every 2 hours were admitted to the PICU. We found that pediatric LABA use in combination with ICS did not increase the likelihood of PICU admission compared to ICS alone, even after adjusting for demographics, asthma severity, history of ICU admissions and concurrent respiratory infection.

An FDA meta-analysis of 110 trials and 60,954 patients found no deaths or intubations associated with single-device combinations of LABA and ICS.[15] While we also observed no deaths, 2 patients on LABA/ICS were intubated compared to no patients on ICS alone.

One surprising finding from our analysis was the poor adherence to guidelines in choosing controller therapy for children with asthma. Almost two thirds (23/35) of patients with documented mild-persistent and moderate-severe persistent were on no controller medicine, and 15% (4/26) of patients on ICS/LABA combination therapy had intermittent asthma. The reason so many patients with persistent asthma were not on controller therapy is unknown, but could include poor adherence to prescribed therapy, inability to afford prescribed therapy and poor recognition of asthma severity by patients/parents and care providers. As for use of combination ICS/LABA therapy in patients with intermittent asthma, data were collected prior to the promulgation of the FDA "black-box" warning for LABA. Together, our data emphasize the need to frequently review asthma severity and provide appropriate controller therapy.

Both the Serevent National Surveillance (SNS) and Salmeterol Multicenter Asthma Research Trial (SMART) studies, each including more than 25,000 patients, suggested a three to four-fold increase in the risk of death with LABA use compared to controls.[2,3] Post-hoc analysis of SMART suggested that the increased risk was limited to those not prescribed ICS, a treatment regimen now clearly recognized to be unsafe.**[14, 22=24] Neither SNS nor SMART was designed to assess the risk of death with combined LABA/ICS use. The feasibility of a randomized trial to assess this issue is controversial. A study designed to rule out a twenty-percent increase in mortality would require approximately 700,000 patients.[4,5] Utilizing an alternative sample size calculation for such a trial, Kazani *et al.* proposed that a study of 50,000 patients with moderate-severe persistent asthma would have the power to detect or exclude a four-fold or greater increase in likelihood of death.[4] In contrast, a case-control study would require significantly less patients, from less than 500 to several thousand, based on a ration of cases to controls of 1:5 and depending on power, relative risk with LABA use, and the frequency of LABA/ICS combination therapy use the target population.[5]

To help address this issue in children, we used the likelihood of PICU admission as a surrogate outcome of near-fatal asthma in children on LABA/ICS compared to those on ICS alone. Our study was powered to detect greater than a two to three-fold increased likelihood of PICU admission. The validity of using the likelihood of PICU admission as a surrogate outcome is enforced by consistent asthmatic PICU admission criteria.

Limitations of this study include those inherent in all retrospective chart-review case-control studies. There was minimal information regarding duration of therapy duration or medication compliance. Appropriate control and reference group selection is particularly important in case-control studies. We chose pediatric medical floor admission as controls due to more complete documentation than emergency department visits. Because all patients were admitted and no outpatient subjects were included, findings in this study are only generalizable to a population of children with an asthma exacerbation requiring at least admission to the hospital. Of course, patients with poorly-controlled asthma are those for whom combination therapy is typically recommended.

Potential confounders can be a major obstacle to the validity of case-control studies, and incomplete documentation of those variables can be a significant problem. We used a systematic method to choose potential confounders to include in our logistic regression model. We accounted for missing data of a potential confounder by using ICS dose to estimate asthma severity, in addition to direct documentation. The adjusted odds ratios for both logistic regression analyses were similar. In addition, we performed a stratification analysis for each asthma severity classification.

Conclusions

Utilizing PICU admission as a surrogate for life-threatening asthma exacerbation, a maintenance regimen consisting of LABA/ICS did not appear to increase the likelihood of near-fatal asthma compared ICS alone in children in either crude or adjusted analyses.

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Table 1

Baseline demographic and socioeconomic characteristics for asthmatics admitted to the pediatric intensive care unit versus pediatric medical floor (n = 181).

Characteristics	PICU Admission	PMF Admission	
	n (%)	n (%)	*p*[a]
Total patients	85 (47.0)	96 (53.0)	
Mean age	9.4 ± 0.4	8.3 ± 0.4	0.977
Age categories			0.273
Age 4–7	34 (40.0)	47 (49.0)	
Age 8–11	26 (30.6)	24 (25.0)	
Age 12–15	15 (17.7)	20 (20.8)	
Age 15–18	10 (11.8)	5 (5.2)	
Sex			0.074
Male	41 (48.2)	59 (61.5)	
Female	44 (51.8)	37 (38.5)	
Race			0.305
White	44 (51.8)	49 (51.0)	
Black	31 (36.5)	41 (42.7)	
Hispanic	1 (1.2)	0 (0.0)	
Asian	1 (1.2)	3 (3.1)	
Other	2 (2.4)	0 (0.0)	
Unknown	6 (7.1)	3 (3.1)	
Access to subspecialty care	23 (27.1)	26 (27.1)	0.997
Medicaid	41 (48.2)	57 (59.4)	0.133

[a]The p-value for a chi-square test.

Table 2

Baseline asthma history, severity and risk factors for asthmatics admitted to the pediatric intensive care unit versus pediatric medical floor (n = 181).

Characteristics	PICU Admission	PMF Admission	
	n (%)	n (%)	*p*[a]
Total patients	85 (47.0)	96 (53.0)	
History of asthma	79 (92.9)	89 (92.7)	0.952
Asthma severity [b]			0.706
Intermittent	31 (36.9)	38 (40.4)	
Mild persistent	13 (15.5)	17 (18.1)	
Moderate-severe persistent	40 (47.6)	39 (41.5)	
History of floor admission	52 (68.4)	50 (61.7)	0.380
History of ICU admission	19 (25.0)	7 (8.6)	0.006
History of intubation	7 (9.2)	2 (2.5)	0.069
Home asthma medication			0.612
No controller medication	40 (52.0)	39 (44.3)	
ICS only	19 (24.7)	26 (29.6)	
LABA/ICS	18 (23.4)	23 (26.1)	
Montelukast only	23 (27.1)	28 (29.2)	0.753
Allergic rhinitis	45 (60.0)	50 (60.2)	0.975
Atopic dermatitis	14 (18.7)	15 (18.1)	0.923
Food allergies	8 (10.7)	6 (7.2)	0.448
Pet exposure	32 (59.3)	27 (54.0)	0.589
Smoke exposure	29 (53.7)	26 (52.0)	0.862

[a]The p-value for a chi-square test.

[b]Categorical variable of asthma severity based on combination of documentation and estimate from ICS dose.

Table 3

Asthma exacerbation characteristics for asthmatics admitted to the pediatric intensive care unit versus pediatric medical floor (n = 181).

Characteristics	PICU Admission	PMF Admission	
	n (%)	n (%)	*p*[a]
Total patients	85 (47.0)	96 (53.0)	
Upper respiratory infection	52 (61.2)	76 (79.2)	0.008
Chest x-ray			<0.001
None	3 (3.5)	30 (31.3)	
Normal	27 (31.8)	31 (32.3)	
Hyperinflation	14 (16.5)	5 (5.2)	
Atelectasis	16 (18.8)	7 (7.3)	
Pneumothorax	2 (2.4)	1 (1.0)	
Infiltrate	21 (24.7)	21 (21.9)	
Effusion	2 (2.4)	1 (1.0)	
Antibiotics	42 (49.4)	37 (38.5)	0.141
Atypical organisms	41 (48.2)	27 (28.1)	0.005
Typical organisms	30 (35.3)	18 (18.8)	0.012
Corticosteroids	85 (100.0)	96 (100.0)	

[a]The p-value for a chi-square test.

Table 4

Asthma admission outcomes for children on ICS only, LABA/ICS and no controller medication (n = 181).

Outcomes	ICS only	LABA/ICS	No controller medication	
	n (%)	n (%)	n (%)	*P*
PICU admission	19 (42.2)	18 (43.9)	40 (53.6)	0.612[a]
Death	0 (0.0)	0 (0.0)	0 (0.0)	
Intubation	0 (0.0)	2 (4.9)	3 (3.8)	0.447[b]
CPAP or BiPAP[c]	2 (4.4)	1 (2.4)	0 (0.0)	0.139[b]

[a]The p-value for a chi-square test.

[b]The p-value for a Fisher's exact test (for rare events).

[c]Continuous or bilevel positive airway pressure

Table 5

Logistic regression analysis for PICU admission in asthmatics on LABA/ICS or no controller medication compared to patients on ICS only (n = 165).

PICU Admission[c]		Unadjusted	Adjusted[a]	Adjusted[b]
	n	OR (95% CI)	aOR (95% CI)	aOR (95% CI)
		n = 165	n = 132	n = 86
Home Asthma Medication[d]				
ICS only	45	Reference	Reference	Reference
ICS/LABA	41	1.07 (0.46–2.52)	0.82 (0.25–2.73)	0.35 (0.07–1.79)
No controller medication	79	1.40 (0.67–2.94)	2.15 (0.67–6.87)	1.44 (0.33–6.31)

[a]Covariates in logistic regression model are age, sex race, severity (based on combination of documentation and estimate from ICS dose), history of ICU admissions and respiratory infection.

[b]Covariates in logistic regression model are age, sex, race, severity (strictly from documentation only), history of ICU admissions and respiratory infection.

[c]Binary outcome variable with reference group of PMF admissions, OR was calculated using binary logistic regression.

[d]Categorical exposure variable with reference group of ICS only.