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Salmeterol Use and Risk of Admission among Emergency Department Patients with Acute Asthma

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Abstract

Background—The safety of inhaled long-acting 2-agonists (LABA) in chronic asthma management remains controversial and has not been evaluated in emergency department (ED) patients with acute asthma.

Objective—We hypothesized that ED patients on chronic LABA therapy would have increased risk of asthma-related hospitalization compared to those not on LABA therapy, and that concurrent chronic inhaled corticosteroid (ICS) therapy would mitigate this risk.

Methods—Prospective cohort study of patients age 12–54 with acute asthma in 115 EDs. Four patient groups were created based on their chronic asthma regimen: (A) no ICS or salmeterol; (B) salmeterol monotherapy; (C) ICS monotherapy; and (D) combination ICS and salmeterol.

Results—Of the 2,236 included patients, Group A had 1,221 (55%) patients; B 48 (2%); C 787 (35%); and D 180 (8%); 489 (22%) patients required hospitalization. In a multivariable model controlling for 20 factors and using Group A as the reference, Group B had an increased risk of hospitalization (OR 2.2; 95%CI, 1.0–4.9), while Groups C (OR 1.1; 95%CI, 0.8–1.5) and D (OR 1.2; 95%CI, 0.8–1.9) did not.

Conclusion—Among ED patients with acute asthma, those on salmeterol monotherapy had an increased risk of hospitalization, however this risk was not seen among patients on combination ICS-salmeterol therapy. Our findings provide data from a unique ED population on clinical response to acute asthma treatment among patients on chronic LABA therapy.

Keywords

Asthma; Emergency department; Long-acting β_2 -agonists; Asthma exacerbation; Salmeterol

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INTRODUCTION

Approximately 23 million people currently have asthma in the United States (7.8% prevalence), and they account for 1.8 million emergency department (ED) visits and nearly 500,000 hospitalizations for asthma each year.^{1, 2} Additionally, over \$2 billion is spent on asthma hospitalizations each year, which represents nearly 17% of all asthma-related costs.³ Episodes of acute asthma, and their response to rescue treatment, provide insight into the risk of serious asthma-related adverse events and fatal asthma. Furthermore, the ED is a common setting for the initial presentation of moderate and severe asthma exacerbations.^{4, 5}

A recent Food and Drug Administration (FDA) review panel has re-ignited a more than decade-long debate on the safety of inhaled long-acting β_2 -agonists (LABA) in the management of asthma.^{6–8} LABA monotherapy is not recommended in chronic asthma management because of its reported association with near-fatal or fatal events.^{4, 9–12} However, there remains an ongoing debate regarding the safety of chronic LABA use when combined with inhaled corticosteroid (ICS) therapy,^{6, 7} and specifically, whether the addition of ICS to LABA therapy mitigates the possible adverse effects of LABA monotherapy. Among the postulated harmful mechanisms, LABA monotherapy may increase sensitivity to bronchoconstricting stimuli, mask symptoms of chronic asthma severity, and induce tolerance to short-acting β_2 -agonist (SABA) rescue therapy in the acute setting.^{7, 13–15} If chronic LABA therapy worsens the response to bronchoconstricting stimuli, delays recognition of acute asthma, or causes a tolerance to rescue SABA therapy, the need for hospitalization during episodes of acute asthma would likely increase.

Most randomized controlled trials (RCT) of asthma therapy have studied outpatients with asthma. However there is a growing appreciation that the patients with acute asthma commonly represent a sicker cohort and a different treatment perspective than typical asthma outpatients.^{16–18} Additionally, asthma-related hospitalization is more common in an ED cohort with acute asthma, ranging from 15–25%,^{19, 20} compared to the approximately 2% annual incidence seen in typical RCT study populations.¹² Therefore, by evaluating the association of chronic LABA therapy and hospitalization in a large number of ED patients with acute asthma, we hope to gain insight into the response to acute treatment and safety of LABA in this important and unique setting. To our knowledge, this approach has not been used to examine this important issue. We hypothesized that ED patients with acute asthma on chronic salmeterol monotherapy would have increased risk of hospitalization compared to those not on salmeterol therapy, and that concurrent chronic ICS therapy would mitigate this increased risk.

METHODS

This study combines data from several prospective cohort studies performed during 1996 to 2001, as part of the Multicenter Airway Research Collaboration. The collaboration is part of the Emergency Medicine Network (EMNet), a clinical research collaboration with 204 participating EDs.²¹ Using a standard protocol, investigators at 115 EDs in 25 US states and 6 Canadian provinces enrolled patients 24-hours per day for a median of two weeks.¹⁷ All patients were managed at the discretion of the treating physician. Inclusion criteria were physician diagnosis of acute asthma; age 12–54; and the ability to give informed consent. Repeat visits within the study period were excluded from the current study. Of note, formoterol was approved for use in 2001, thus salmeterol was the only FDA-approved LABA during our study period. The Institutional Review Board at each of the 115 participating hospitals approved the study, and written informed consent was obtained from all participants.

Data Collection

The ED interview assessed patients' demographic characteristics, asthma history, and details of their current asthma exacerbation including duration of symptoms, number of inhaled short-acting β -agonist puffs within 6 hours of ED arrival, severity of symptoms, respiratory rate, O_2 saturation, and peak expiratory flow (PEF). Data on ED management and disposition were obtained by chart review. All forms were reviewed by site investigators before submission to the EMNet Coordinating Center in Boston, where they underwent further review by trained personnel and then double data entry.

Median family income was estimated using patients' home ZIP codes.^{22, 23} Primary care physician (PCP) status was assigned on the basis of the following question: "Do you have a primary care provider (such as a family doctor, internist, or nurse practitioner)?" PEF is expressed as percentage of patient's predicted value, based on race, age, gender, and height.²⁴

Patients were divided into four treatment groups based on self-reported medication use during the four weeks before their ED visit: Group A reported that they had not used ICS nor salmeterol; Group B reported use of salmeterol but not ICS (i.e., salmeterol monotherapy); Group C reported use of ICS but not salmeterol (i.e., ICS monotherapy); and Group D reported use of both ICS and salmeterol (i.e., combination ICS-salmeterol therapy). This analysis was restricted to 2,236 patients with complete information on recent medication use and all 20 sociodemographic, chronic asthma, and acute asthma factors included in the final multivariable models. The main results did not materially differ when analyses were repeated in the larger cohort with missing data for one or more of the 20 required covariates (data not shown).

Statistical Analysis

All analyses were performed using Stata 10.0 (StataCorp, College Station, TX). Associations between the four treatment groups and other characteristics of interest were examined using Chi-square test, Student's t-test, and Wilcoxon rank sum test, as appropriate. Multivariable logistic regression was used to assess the association between treatment group and hospital admission. The primary models use Group A as the reference group, but we also explored Group C (i.e., ICS monotherapy) as reference. All odds ratios (OR) and β -coefficients are shown with 95% confidence intervals (CI). All p-values are two-tailed with $P < 0.05$ considered statistically significant.

RESULTS

Among 3,306 eligible patients, 3,260 (99%) had information on recent medication usage, and 2,236 (68%) had information on all 20 factors included in the final multivariable model. As shown in Table 1, Group A had 1,221 (55%) patients; Group B had 48 (2%) patients; Group C had 787 (35%) patients; and Group D had 180 (8%) patients. The mean age of the cohort was 34 years and 65% were female. Overall, 47% were non-Hispanic black, 28% were non-Hispanic white, and 23% were Hispanic; 67% reported having a PCP. A total of 489 (22%) patients required hospitalization for their asthma exacerbation.

The four treatment groups differed across many sociodemographic factors, including age, sex, race, education, and insurance status (Table 1). Patients in Group A were younger, while patients in Group B were more likely to be female. Patients in Group D were more likely to be Non-Hispanic white and were more likely to have private insurance. As expected, combination ICS-salmeterol therapy was more common during the later years of the 5-year study period.

Chronic asthma factors also differed across treatment groups (Table 2). As expected, patients in Group D had more ED visits during the past year, were more likely to be admitted for asthma

during the past year, and were more likely to report taking inhaled SABA and systemic steroids during the 4 weeks prior to the ED visit.

Acute asthma characteristics and ED management are shown in Table 3. While the groups differed by number of SABA puffs before ED arrival, they did not differ by initial PEF. In the ED, those in Group D were most likely to receive systemic steroids. Although the four treatment groups had similar final PEF, the ED length-of-stay was shortest in Group A and longest in Group D. Patients in Group D, who had the worst chronic asthma severity, were most likely to be admitted in the unadjusted analysis.

Table 4 shows multivariable models assessing the association between medication use and hospital admission. The unadjusted model showed that patients in Group B had an increased risk of hospital admission compared to those in Group A (reference group). Groups C or Group D also appeared to be at increased risk for hospital admission compared to Group A in the unadjusted analysis. The findings for Group C and Group D did not change when controlling for sociodemographic factors. However, the addition of chronic asthma factors to the multivariable model attenuated this observation, which is likely attributable to the higher chronic asthma severity in these groups. Finally, adding acute asthma factors to the model eliminated the increased admission risk for Group C and Group D. By contrast, the full multivariable model revealed an increased risk of hospital admission in Group B. Model fit and area under the receiver operating characteristic curve was best in the full multivariable model (Table 4). When the reference group was changed to Group C, similar findings resulted. In the full multivariable model, Group D again showed no significant risk of hospital admission (OR 1.1; 95%CI 0.7–1.7), however there was a trend towards an increased risk of hospital admission in Group B (OR 2.0; 95%CI 0.9–4.5) compared to Group C.

DISCUSSION

ED patients with acute asthma are an important subgroup of asthma patients with relatively high risk of adverse outcomes. Given the continued concerns over the safety of chronic LABA therapy, it is important to examine this issue in this unique population. In our large multicenter prospective cohort of ED patients with acute asthma, we found an increased risk of hospitalization among patients on salmeterol monotherapy, but no apparent increased risk among patients on combination ICS-salmeterol therapy. We used multivariable logistic regression to control for the different sociodemographic, chronic asthma, and acute asthma factors between the groups. This is a common statistical method used in observational studies to adjust for potential confounders.²⁵ An important observation is that prior to adjustment, the combination ICS-salmeterol therapy patients (Group D) appeared to have the highest risk of hospitalization; however after adjustment, the majority of this group's hospitalization risk was explained by confounding factors. Conversely, even after adjusting for confounders, the salmeterol monotherapy patients (Group B) still showed a higher risk of hospitalization. To our knowledge, only one prior study has examined this issue but was limited by small sample size (n=114) at a single site, lacked adjustment for potential confounders, and lacked patients on ICS therapy.²⁶ Thus, our study adds novel data to the ongoing debate from the ED setting.

The consistent message about LABA – from the Salmeterol Multicenter Asthma Research Trial (SMART) trial¹¹ and four subsequent meta-analyses^{9, 10, 12, 27} – is that LABA increases the risk of fatal asthma as compared to treatment with placebo. Furthermore, two of three meta-analyses showed that risk of asthma-related hospitalization is also increased on LABA compared to placebo.^{9, 10, 12} Although these risks are largely attributed to the effects of LABA monotherapy, it is important to recognize that the majority of trials allowed patients to be on concurrent baseline ICS therapy, including the SMART trial which heavily weighted all subsequent meta-analyses.⁹ Post-hoc analysis of SMART data and one meta-analysis do

support that LABA monotherapy is the likely culprit for fatal asthma,^{11, 27} however such conclusions based on secondary analyses should be accepted cautiously. Additionally, asthma-related hospitalization has not been similarly examined. Common hypotheses to explain why chronic LABA monotherapy may increase asthma-related hospitalizations include tolerance to rescue SABA therapy, increased sensitivity to bronchoconstricting stimuli, and masking of acute asthma symptoms resulting in delayed presentation.^{7, 13–15} These proposed mechanisms would lead to decreased asthma control in the ED setting, necessitating hospitalization for further management. Indeed, when we focused on ED patients with acute asthma, we also found an increased risk of hospitalization in patients on salmeterol monotherapy.

More controversial is the question of whether combination therapy with ICS can protect against the adverse effects of LABA.^{6, 7} Recent meta-analyses have reported no risk difference in asthma-related hospitalization between combination ICS-LABA therapy compared to ICS monotherapy.^{9, 12, 28–32} Likewise, in our ED cohort, patients on chronic combination ICS-salmeterol therapy did not experience increased risk of asthma-related hospitalization, as was found in the salmeterol monotherapy group. Importantly, when we changed our reference group to ICS monotherapy, combination ICS-salmeterol therapy continued to show no difference in the risk of hospitalization. Therefore, it appears that the apparently protective effects of ICS in combination therapy, as reported in several population-based asthma outpatient studies,^{9, 12, 28–32} also applies to high-risk ED patients with acute asthma.

Two recent meta-analyses have suggested a beneficial effect of combination ICS-LABA therapy compared to ICS monotherapy.^{9, 28} In 2008, Jaeschke and colleagues reported a meta-analysis that looked at 62 RCTs.²⁸ Only 34 RCTs had results on asthma-related nonfatal hospitalization and of these 18 RCTs used similar baseline ICS dosages. They found a trend towards a beneficial effect of combination ICS-LABA therapy, both when they looked at similar dosages of baseline ICS between groups (OR 0.66; 95%CI 0.41–1.05) and differing dosages of ICS (OR 0.74; 95%CI 0.53–1.03). In a 2009 meta-analysis, Rodrigo and colleagues found 57 RCTs comparing combination ICS-LABA therapy versus ICS monotherapy, of which 25 RCTs reported outcomes for asthma-related hospitalizations.⁹ They found a significant beneficial effect of combination therapy for risk of asthma-related hospitalization (RR 0.58; 95%CI 0.45–0.74).

While these two meta-analyses^{9, 28} suggest a potential beneficial effect of combination therapy, our study did not show a similar trend or difference. It could be that our study was underpowered to detect this difference. Additionally the differences in our population of acute asthma patients compared to the asthma outpatients in RCTs may be important. In the setting of acute asthma, it could be possible that no additional benefit of combination therapy exists, but that the benefit actually resides in the prevention rather than the treatment of acute asthma episodes. These possibilities merit further study.

Regardless, current recommendations of the National Asthma Education and Prevention Program (NAEPP) state that LABA should not be used as monotherapy and should only be added to concurrent ICS therapy in the setting of moderate-to-severe persistent asthma.⁴ Recent meta-analyses have provided much evidence in support of this approach in the chronic management of asthma. Our study adds evidence on the safety of combination ICS-salmeterol therapy in a large population of ED patients with acute asthma and suggests that the NAEPP guidelines remain relevant in this important setting.

Potential Limitations

Our study was ED-based, and not population-based, so care must be taken when generalizing these results to other clinical settings or to the clinical course of less severe episodes of acute asthma. However, given that the concern about salmeterol relates to an increased risk of fatal

and near-fatal events, we believe that the ED setting provides valuable insight into this contentious issue. Additionally, our analysis is based on observational studies, not randomized trials. While we used multivariable modeling techniques and stratification to control for observed differences in acute and chronic asthma severity, there is always the possibility of unmeasured confounding.³³ The final multivariable model, however, had a relatively high area-under-the-curve (0.86) and did eliminate the apparent increased risk of those on ICS and combination ICS-salmeterol therapy. We did not collect data on forced expiratory volume in one second or daytime and nighttime symptoms. Our study may have enrolled patients who were not optimized on their chronic asthma medications or not on appropriate preventative medications. This would likely result in a higher severity of acute asthma, thus we anticipate bias related to this subset of patients would be minimized by our adjusting for acute asthma severity. It is often difficult to distinguish asthma from other chronic obstructive pulmonary diseases, thus it is possible patients were misclassified as asthma in our study; however, using a younger age range for our inclusion criteria would minimize this limitation and our adjusting for age and smoking status would further minimize significant bias. Lastly, we recognize that our study did not have a standardized treatment protocol or admission criteria. This could result in increased variability in our measured outcome or add bias to our results. However, increased variability would favor a null result, while bias was minimized by adjusting for severity and acute ED management.

Conclusion

ED patients with acute asthma represent a high risk population, and we examined the safety of LABA in this unique setting. Our study shows that LABA monotherapy is associated with an increased risk of asthma-related hospitalization, while concurrent chronic therapy with ICS appears to protect against this risk. While our findings remain consistent with prior studies, we provide further evidence that combination ICS-LABA therapy remains safe even in high risk acute asthma. Hospitalization remains an important outcome in acute asthma for its relation to acute asthma severity, including response to emergency treatment; its association with future morbidity and mortality; and its implication for healthcare costs. Our study results from the ED setting reinforce the importance and safety of following NAEPP guidelines for the chronic management of asthma.

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ABBREVIATIONS

ED	emergency department
FDA	Food and Drug Administration
LABA	long-acting β_2 -agonist
ICS	inhaled corticosteroid
SABA	short-acting β_2 -agonist
RCT	randomized controlled trial
EMNet	Emergency Medicine Network
PEF	peak expiratory flow
PCP	primary care provider
OR	odds ratio

CI	confidence interval
NAEPP	National Asthma Education and Prevention Program

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Table 1
Sociodemographic Characteristics of Asthma Patients Treated in the Emergency Department, According to Chronic Medication.

	No ICS No Salmeterol (n = 1221)	No ICS Salmeterol Use (n = 48)	ICS Use No Salmeterol (n = 787)	ICS Use Salmeterol Use (n = 180)	P value
Age, mean ± SD	32 ± 11	36 ± 12	36 ± 11	36 ± 11	<0.001
Sex (%)					<0.001
Male	40	19	31	27	
Female	60	81	69	73	
Race/ethnicity (%)					0.01
Non-Hispanic White	25	29	30	37	
Non-Hispanic Black	48	52	45	46	
Hispanic	25	15	22	16	
Other	2	4	3	2	
Primary care provider (%)	58	79	79	83	<0.001
Insurance (%)					<0.001
Private/HMO/commercial	28	31	30	36	
Medicaid	26	31	31	25	
Other public	9	10	15	18	
None	36	27	24	21	
High school graduate (%) [*]	68	65	69	79	0.02
Estimated household income, median (IQR)	28,882 (20,696–8,257)	29,283 (24,630–6,250)	29,497 (20,346–0,191)	33,111 (23,056–1,608)	0.006
Year of enrollment (%)					<0.001
1996	21	13	23	8	
1997 – 1998	49	40	50	42	
1999 – 2001	30	48	27	49	

ICS denotes inhaled corticosteroids; SD, standard deviation; HMO, health maintenance organization; IQR, interquartile range.

^{*} Patient's education level for patients age 18–54 (n=2,057); parent's education level for patients age 12–17 (n=179).

Table 2

Chronic Asthma Characteristics of Asthma Patients Treated in the Emergency Department, According to Chronic Medication.

	No ICS No Salmeterol (n = 1221)	No ICS Salmeterol Use (n = 48)	ICS Use No Salmeterol (n = 787)	ICS Use Salmeterol Use (n = 180)	P value
Current smoker (%)	38	21	29	22	<0.001
Inhaled SABA use in past 4 wks (%)	76	90	96	99	<0.001
Home nebulizer usage (%)	21	24	40	63	<0.001
Ever hospitalized for asthma (%)	51	63	73	83	<0.001
Ever intubated for asthma (%)	10	17	19	27	<0.001
Hospitalized for asthma in past year (%)	17	27	40	51	<0.001
No. of ED visits for asthma in past year, median (IQR)	1 (0 – 3)	2 (0 – 4)	3 (1 – 6)	3 (1 – 10)	<0.001
No. urgent clinic visits for asthma in past year, median (IQR)	0 (0 – 1)	0 (0 – 2)	1 (0 – 4)	2 (0 – 6)	<0.001
Systemic steroid use in past 4 wks (%)	13	33	37	48	<0.001
Chronic systemic steroid use (%)	2	10	9	16	<0.001
Concomitant medical disorder (%)	7	8	8	11	0.15
COPD (%) *	1	2	3	2	0.17

SABA denotes short-acting β_2 -agonist; ICS, inhaled corticosteroids; ED, emergency department; IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

* Among patients 18–54 (n=2,057).

Table 3

Acute Asthma Characteristics and Emergency Department Management of Asthma Patients Treated in the Emergency Department, According to Chronic Medication.

	No ICS No Salmeterol (n = 1221)	No ICS Salmeterol Use (n = 48)	ICS Use No Salmeterol (n = 787)	ICS Use Salmeterol Use (n = 180)	P value
Duration of symptoms <24 hours (%)	53	52	52	47	0.52
No. SABA puffs in 6 hours before ED arrival, median (IQR)	2 (0 – 8)	4 (2 – 9)	6 (2 – 16)	10 (4 – 24)	<0.001
Initial Peak Flow (%)					0.16*
≥ 70	12	13	14	12	
≥ 50 – 69	18	17	24	13	
< 50	39	38	39	40	
Final Peak Flow (%)					0.54*
≥ 70	43	42	44	39	
≥ 50 – 69	21	23	21	22	
< 50	12	17	15	17	
Given systemic steroids (%)	69	60	76	81	<0.001
No. inhaled SABA treatments over entire ED stay, median (IQR)	3 (2 – 4)	3 (2 – 4)	3 (2 – 4)	3 (2 – 5)	<0.001
ED length of stay (min), median (IQR)	180 (125 – 259)	206 (161 – 320)	194 (135 – 287)	210 (153 – 301)	<0.001
ED disposition (%)					<0.001
Sent home	83	71	73	67	
Observation	3	8	3	4	
Admit regular	12	21	21	28	
Admit ICU	2	0	3	2	

SABA denotes short-acting β_2 -agonist; ICS, inhaled corticosteroids; IQR, interquartile range; ED, emergency department.

* Mean values within a cell are expressed in L/min. P-values were calculated after exclusion of missing and unknown values.

Table 4

Multivariable Model of the Association between Chronic Asthma Medications and Hospital Admission with No ICS or Salmeterol Usage as the Reference.

	No ICS No Salmeterol (n = 1221; 203 admitted)	No ICS Salmeterol Use (n = 48; 14 admitted)	ICS Use No Salmeterol (n = 787; 212 admitted)	ICS Use Salmeterol Use (n = 180; 60 admitted)
Model 1 [*]	1.0 (Reference)	2.1 (1.1 – 3.9)	1.8 (1.5 – 2.3)	2.5 (1.8 – 3.5)
Model 2 [†]	1.0 (Reference)	1.8 (1.0 – 3.5)	1.6 (1.3 – 2.0)	2.3 (1.6 – 3.4)
Model 3 [‡]	1.0 (Reference)	1.7 (0.8 – 3.3)	1.2 (0.9 – 1.5)	1.4 (0.9 – 2.0)
Model 4 [§]	1.0 (Reference)	2.2 (1.0 – 4.9)	1.1 (0.8 – 1.5)	1.2 (0.8 – 1.9)

ICS denotes inhaled corticosteroids, ROC, receiver operator curve.

^{*} Model 1 is the unadjusted model. *Model fit*: Hosmer-Lemeshow test, 1.0; Area under ROC, 0.59.

[†] Model 2 controls for 9 factors (age, sex, race/ethnicity, education, estimated median household income, year of enrollment, primary care provider status, insurance status, smoking status). *Model fit*: Hosmer-Lemeshow test, 0.36; Area under ROC, 0.64.

[‡] Model 3 controls for above plus 4 chronic asthma factors (ever intubated for asthma, hospitalized for asthma during past year, use of a home nebulizer, chronic systemic steroid use). *Model fit*: Hosmer-Lemeshow test, 0.58; Area under ROC, 0.69.

[§] Model 4 controls for above plus 7 acute asthma factors (number of short-acting β_2 -agonist puffs during 6 hours before ED arrival, duration of symptoms, initial percent-predicted peak expiratory flow rate, number of short-acting β_2 -agonist treatments over entire ED stay, given systemic steroid treatment in ED, final percent-predicted peak expiratory flow rate, ED length of stay). *Model fit*: Hosmer-Lemeshow test, 0.82; Area under ROC, 0.86.