Regular Use of Corticosteroids and Low Use of Short-Acting ß2-Agonists Can Reduce Asthma Hospitalization

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Regular Use of Corticosteroids and Low Use of Short-Acting β_2-Agonists Can Reduce Asthma Hospitalization*

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Objectives: **Inhaled corticosteroids (ICS) and inhaled short-acting β_2-agonists (ISABA) are the most commonly used medications for management of asthma. Increased asthma morbidity and mortality have been reported with excess use of ISABA in several studies. In these studies, authors have used different indicators to control for the potential confounding by asthma severity. The objective of this study was to determine the effect of ICS use on the association between use of ISABA and first hospitalization for asthma after controlling for several indicators of asthma severity.**

Design: **An inceptional cohort study using Saskatchewan Health databases.**

Setting: **The Province of Saskatchewan, Canada.**

Participants: **A total of 29,957 persons aged 5 to 54 years who had at least five asthma-related visits to physicians between 1991 and 2000.**

Results: **Among the subjects with increased asthma severity, indicated by one or more average number of asthma-related physician visits per 3 months during the follow-up, high use of ISABA was a risk factor for hospitalization when no ICS were used (rate ratio [RR], 2.16; 95% confidence interval [CI], 1.51 to 2.95). There was a beneficial effect of ISABA when there was low use of ICS (RR, 0.65; 95% CI, 0.42 to 0.93) or high use of ICS (RR, 0.23; 95% CI, 0.12 to 0.41). Among the subjects with less severe asthma, indicated by less than one asthma-related physician visits per 3 months, on average, during the follow-up, the risk of hospitalization was even greater for high use of ISABA when no ICS were used (RR, 10.06; 95% CI, 6.99 to 14.47). This was reduced but not abolished when there was low use of ICS (RR, 3.24; 95% CI, 2.29 to 4.59) and negated altogether by high use of ICS (RR, 1.10; 95% CI, 0.39 to 3.12).**

Conclusion: **Among both severe and less severe asthma groups, high use of ISABA was associated with an increased risk of asthma hospitalization in the absence of any use of ICS, which was progressively reduced with low and high use of ICS. This finding was independent of asthma severity and could result from lack of control through over reliance on ISABA in asthma management.** ***(CHEST 2005; 127:1242–1251)***

Key words: asthma; hospitalization; inhaled corticosteroids; management; medications; short-acting β_2-agonists

Abbreviations: CI = confidence interval; DPI = dry powder inhaler; ED = emergency department; HMO = health maintenance organization; ICS = inhaled corticosteroids; ISABA = inhaled short-acting β_2-agonists; LABA = long-acting β_2-agonists; MDI = metered dose inhaler; RR = rate ratio; SABA = short-acting β-agonists

Inhaled corticosteroids (ICS) and inhaled short-acting β_2-agonists (ISABA) are the most commonly used asthma medications in children and adults.[1–3] ICS are anti-inflammatory agents and are recommended as first-line therapy in the treatment of asthma in Canada[1,2] and the United States.[3] The beneficial effect of ICS in reducing asthma morbidity and mortality is described in a review article.[4] Regular use of ICS was associated with reduction in asthma-related emergency department (ED) visits,[5] hospital admissions,[6–8] readmissions,[8,9] and

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death.[10–12] Early use of ICS following the initial diagnosis of asthma was shown to be preventive of asthma hospitalization.[13] ISABA are bronchodilators that are recommended only for use as needed.[1–3] Negative effects of ISABA on asthma morbidity and mortality have been highlighted.[14] Increased use of ISABA was associated with increases in asthma-related intensive care admissions,[15] hospital admissions,[16] and death or near death.[12,17–22] In another study,[23] increased use of ISABA was associated with increases in health-care utilization, including physician visits, ED admissions, and hospital admissions for respiratory conditions. To the best of our knowledge, only one study[6] has investigated the risk of asthma hospitalization associated with excess use of ISABA with and without the use of ICS. The study was limited to asthma patients from a health maintenance organization (HMO), and the number of prescriptions was used to indicate low and high use of ISABA.[6]

In our study, we used a population-based health database to identify asthma patients without any previous hospitalization and monitored them up to 10 years to investigate the risk of first asthma hospitalization associated with use of ISABA and ICS after controlling for indicators of severity. We used the quantity and strength of prescriptions to define low and high use of ISABA and ICS.

Materials and Methods

Saskatchewan Health Databases

The Province of Saskatchewan has a population of approximately 1 million people, comprised of persons of European origin (81.7%), aboriginal origin (11.4%), and other single (2.3%) and multiple (4.7%) origins.[24,25] Almost all residents of Saskatchewan (99%) receive universal health coverage from the Provincial Government. Exceptions include those who are covered by the federal government, *ie*, members of the Royal Canadian Mounted Police, members of the Canadian Forces, and inmates of federal penitentiaries. Each eligible Saskatchewan resident is included in the Person Registry System, a central computer file that contains a unique nine-digit health services number, name, address, sex, date of birth, and dates of health coverage initiation and termination. This central computer file is updated daily for name or address changes, births, deaths, and new arrivals and departures from the Province. Four Saskatchewan Health databases including the Person Registry System, physician services, hospital services, and outpatient prescription drug databases were linked to abstract data for our study. These databases have been used previously to conduct epidemiologic studies.[26]

Data Extraction

The physician services database contains information sent by physicians for payment of medical services rendered to patients. ED visits are captured in this database only when nonsalaried physicians attend to the patients or in situations where contract or salaried physicians participate in shadow billing. All asthma-related visits to physicians between January 1, 1989, and December 31, 2000, were identified from the outpatient physician services database using the three-digit International Classification of Diseases, Ninth Revision code 493. For each visit, residence, date of service, and diagnostic code were also obtained from the physician services database.

The hospital services database includes information on all persons discharged from hospital. Asthma hospitalization history during the study period for identified cases was obtained from the hospital services database using the four-digit International Classification of Diseases, Ninth Revision codes 493.0 (extrinsic asthma), 493.1 (intrinsic asthma), and 493.9 (asthma unspecified). Admission and discharge dates, length of stay, and primary diagnosis were obtained for each hospital admission.

The outpatient prescription drug database includes information on benefit prescription drugs purchased by Saskatchewan residents, except the registered Indian population, which is covered by the Federal Government of Canada. These drugs are listed in the Saskatchewan Formulary, which is maintained by the Drug Plan and Extended Benefits Branch of the Saskatchewan Health Department.[27] Some drugs are listed in the formulary under the exception drug status, which results in information on the use of these drugs being captured in the prescription drug database only when physicians make requests for the exception drug status coverage.[27] Leukotriene modifiers are listed in the formulary under the exception drug status. Under the Prescription Drug Plan, Saskatchewan residents receive benefits from the Provincial Government, which include copayments for drugs when a family exceeds a deductible amount.[28]

Asthma-related prescription drugs purchased by patients during the study period were obtained from the outpatient prescription drug database. The information obtained for each prescription included dispensing date, drug class, drug category, strength, dosage form, and quantity dispensed.

Demographic and health coverage information was obtained for individuals identified in the outpatient physician services database from the Personal Registry System. The information from the four databases was linked using a unique identity number for each person. The prescription drug purchase information of registered Indians is not available in the outpatient prescription drug database and, as a result, this group was excluded from the present study.

Cohort Entry

Three studies[17–19] published between 1990 and 1992 reported significant associations between excessive use of ISABA and asthma death or near asthma death. During this period, new guidelines for asthma management were proposed that included the recommendation that inhaled β_2-agonists should be used on an as-needed basis and ICS should be used as a regular-use therapy.[29] We took the midpoint of the 1990 to 1992 period as the starting point for our study, and used the period from January 1, 1989, to December 31, 1990, as the run-in period. Persons who were covered by Saskatchewan Health during the run-in period were excluded if they had a hospitalization in this period. Persons who were from 5 to 54 years of age on January 1, 1991, and had at least five asthma-related visits to physicians prior to January 1, 1991, entered the cohort on the starting date. We chose five visits in order to increase confidence in the diagnosis of asthma. In addition, additional persons joined the cohort at different time points between January 1, 1991, and December 31, 2000, when they completed five asthma-related visits, or turned 5 years of age following five physician visits for asthma.

End of Follow-up

The end of follow-up was either hospitalization for asthma, end of Saskatchewan Health coverage, or end of the study (December 31, 2000), whichever occurred first. The Saskatchewan Health coverage is terminated when a person dies or moves out of the province.

Study Population

Initially, 35,442 persons in the age group 5 to 54 years with at least five asthma-related physician visits were eligible to enter the inceptional cohort during the study period. Of these, 2,097 persons had at least one hospital admission for asthma between January 1, 1989, and December 31, 1990, and 3,388 persons had at least one hospital admission for asthma prior to turning 5 years of age or completing five asthma-related visits to a physician. These patients were excluded, as the main objective of our study was to examine the association between medication use and the first hospitalization for asthma. Asthma management including medication use would be different between those who had previous hospitalizations and those who did not. By excluding these patients from our study, we have ensured that there was no previous asthma hospitalization for at least 2 years or for the length of time we had information on the individual. After excluding the 5,485 persons with previous hospitalizations, 29,957 persons were considered eligible for the study.

Asthma Medications

Asthma medications were classified as ISABA (fenoterol, salbutamol, terbutaline metaproterenol, isoproterenol, procaterol); oral short-acting β_2-agonists (SABA) [fenoterol, salbutamol, terbutaline, metaproterenol]; long-acting inhaled β_2-agonists (LABA) [salmeterol, formoterol]; methylxanthines (theophylline, aminophylline, oxtriphylline); ipratropium and combinations (ipratropium bromide, ipratropium/salbutamol); ICS (beclomethasone, budenoside, flunisolide, fluticasone, trimacinolone); oral corticosteroids (prednisone, prednisolone); fluticasone propionate and salmeterol xinafoate combination; sodium cromoglycate (cromolyn); nedocromil; and ketotifen. Furthermore, SABA were classified by mode of administration, including metered-dose inhaler (MDI) or dry powder inhaler (DPI), oral or nebulized. Each medication, except for ISABA by MDI or DPI and ICS, was classified as a dichotomous variable (yes/no) to indicate dispensing of at least one prescription during the follow-up. The dichotomous variables were used to adjust for potential confounding effects of these medications in the association between asthma hospitalization and use of inhaled β_2-agonists and ICS. Assessment of ISABA by MDI and DPI and ICS was based on the total milligrams dispensed during the follow-up. Total milligrams was obtained using strength and quantity information provided by the outpatient prescription drug database.

Conversion of ISABA

All inhaled ISABA medications were assumed to be equipotent to salbutamol and were converted to salbutamol MDI equivalent. The average monthly salbutamol equivalent quantity was calculated for MDI and DPI by dividing the total milligrams of salbutamol dispensed during the follow-up by the duration of follow-up (in months). In cases in which follow-up was less than full months, the time was rounded to the nearest greater month; thus, in calculating average monthly dosage, the minimum period of follow-up for a prescription was assumed to be 1 month. The average monthly use of salbutamol equivalent for MDI and/or DPI were then categorized into none, low (less than or equal to one canister salbutamol per month), and high (more than one canister per month) average use, respectively. One canister of salbutamol per month is equivalent to 200 inhalations (100 μg per inhalation) per month or approximately 7 inhalations (700 μg) per day; and according to the National Institutes of Health guidelines, more than one canister use per month is considered to be overreliance on ISABA and inappropriate use of ISABA.[3]

Conversion of ICS

ICS medications were converted to beclomethasone (aerosol) equivalent using the formula suggested by Blais et al.[30] One milligram of beclomethasone for nebulizer solution was assumed to be equivalent to 0.1 mg of beclomethasone by metered-dose aerosol. One milligram of beclomethasone for disk inhaler was assumed to be equivalent to 2 mg of beclomethasone by metered aerosol. In converting other corticosteroid drugs to a beclomethasone equivalent, we assumed that 1 mg of beclomethasone was equivalent to 0.8 mg of budesonide, 0.5 mg of fluticasone, 2.5 mg of flunisolide, and 4 mg of triamcinolone. The average monthly dosage was calculated by dividing the total milligrams of beclomethasone equivalent dispensed during the follow-up by the duration of follow-up (in months), again using 1 month as a minimum follow-up. The average monthly use of ICS was then categorized into none, low (less than or equal to one canister per month), and high (more than one canister per month). One canister of beclomethasone per month is equivalent to 200 inhalations per month (50 μg per inhalation) or approximately seven puffs per day (350 μg). This categorization has been used in a previous study[10] examining the association between the use of ICS and asthma-related death or near death.

Severity Indicators

Use of oral corticosteroids, SABA administered by nebulizers, and number of asthma-related visits to physicians during the follow-up were considered as indicators of severity. Based on the distribution of number of asthma-related physician visits, the average number of visits in a 3-month follow-up period was used to determine asthma severity. Subjects with more than one asthma-related visit per 3 months on average were assigned to the more severe category.

Statistical Analysis

The follow-up period of each subject was expressed in years and used as the contribution to the person-year calculations. The rate of hospitalization per year was determined by the ratio between number of asthma hospitalizations and the total person-years, and was expressed per 1,000 persons per year. The risk of asthma hospitalization was determined by the ratio between hospitalization rates for two levels of a risk factor. The significance of the rate ratios (RRs) was indicated by 95% confidence intervals (CIs). Poisson regression for cohort analysis was used to determine independent risk factors for asthma hospitalization. The GENMOD program in SAS (SAS Institute; Cary, NC) was used for the Poisson regression analysis, with logarithm of number hospitalizations as the dependent variable and total person-years as an offset in the regression model. Factors that were significant at 20% level of significance ($p = 0.20$) in the univariate analysis were considered in the multivariate analysis. After selecting significant factors in the multivariate model, interaction effects were tested for statistical significance. RRs for the factors that were part of the interactions were calculated

using the contribution from main and interaction effects. Likelihood ratio tests were used to determine statistical significance in the univariate and multivariate models. Indicators of severity were included in the multivariate analysis. In addition, a stratified analysis using Poisson regression was conducted to assess if severity was a confounding factor in the relationship between medication use and asthma hospitalization.

Results

Demographic Characteristics

As shown in Table 1, the age distribution of the cohort was skewed to the right with a greater proportion of children 5 to 14 years of age in comparison to the proportion of younger and older adults. These differences in the age distribution resulted in slightly greater proportion of male patients in the cohort because of asthma prevalence being greater in younger boys than girls. Because of the initial run-in period from 1989 to 1990, a higher proportion of persons (28.5%) entered the cohort during 1991 to 1992 than in later periods, during which the proportion of entry into the cohort was almost a constant, varying slightly between 17.5% and 18.5% from 1993 to 2000. The proportion of urban dwellers in the cohort (60.2%) was greater than that of rural dwellers (39.8%), reflecting the population distribution of the Province of Saskatchewan.

Use of Asthma Medications

During the follow-up, the average use of ISABA administered by MDI and/or DPI was greater in younger and older adults than in children 5 to 14 years old (Table 2). Only 1% of the children were receiving high doses in comparison to approximately 7% in younger and older adults. A greater proportion (14.5%) of children received ISABA administered with nebulizer in comparison to younger adults (6.1%) and older adults (8.6%). There was only a slight difference in the total use of ICS between children (63.6%), younger adults (62.7%), and older adults (69.5%). Use of oral corticosteroids was greater in older adults (31.9%) than in younger adults (23.9%) and children (18.4%). Secondary anti-inflammatory medications, sodium cromoglycate and nedocromil, were used at least once by 11.3% and 1.2% of the cohort, respectively. Not surprisingly, a greater proportion of children used sodium cromoglycate than younger and older adult groups, while a greater proportion of older adults used theophylline, oral SABA, and ipratropium combinations. Only a small proportion of the cohort used fluticasone combinations and ketotifen. LABA and leukotriene modifiers were used only by a small proportion of the cohort.

Table 1—*Demographic Characteristics of the Cohort*

Characteristics	No. (%)
Age group at study entry, yr	
5–14	13,874 (46.3)
15–34	9,427 (31.5)
35–54	6,656 (22.2)
Sex	
Male	15,897 (53.1)
Female	14,060 (46.9)
Entry period	
1991–1992	8,525 (28.5)
1993–1994	5,254 (17.5)
1995–1996	5,537 (18.5)
1997–1998	5,413 (18.1)
1999–2000	5,228 (17.5)
Residence	
Urban	18,041 (60.2)
Rural	11,916 (39.8)
Average number of asthma-related visits to physician per 3 mo	
≤ 1	27,840 (92.9)
> 1	2,117 (7.1)

Combined Use of ISABA and ICS

The distribution of average combined use of ISABA administered by MDI and/or DPI, and ICS is illustrated in Figure 1 for the whole cohort. The majority of persons were receiving low doses of these medications. A substantial proportion (21.9%) of the cohort was receiving neither medication during the follow-up. ICS were not used in 13.1% of the cohort receiving low doses of ISABA and in 0.5% of the cohort receiving high doses of ISABA during the follow-up.

Asthma Hospitalization Rates by Demographic Factors

The overall asthma hospitalization rate in this cohort was 15.01 per 1,000 persons per year (Table 3). The median and interquartile range for the length of follow-up was 1.06 years and 2.76 years, respectively, for hospitalized persons and 5.00 and 5.46 years for nonhospitalized persons, respectively. In the univariate analysis shown in Table 3, children and younger adults, male patients, persons entering the cohort between 1993 and 1998, and urban dwellers were less likely to be hospitalized for asthma. Hospitalization rates for persons entering the cohort during from 1991 to 1992 and from 1999 to 2000 were greater than those for the other entry periods. The higher rate for the 1991 to 1992 cohort may be related to the initial run-in period, and the higher rate for the 1999 to 2000 cohort may be related to the shorter potential follow-up for the nonhospitalized persons, and the maximum possible

Table 2—*Age Group-Specific Asthma Medication Use During the Follow-up in Saskatchewan

Medication Use	5 to 14 yr (n = 13,874)	15 to 34 yr (n = 9,427)	35 to 54 yr (n = 6,656)
ISABA (MDI and/or DPI)			
None	5,335 (38.5)	2,269 (24.1)	1,907 (28.7)
Low	8,398 (60.5)	6,491 (68.9)	4,262 (64.0)
High	141 (1.0)	667 (7.1)	487 (7.3)
ICS			
None	5,057 (36.4)	3,518 (37.3)	2,031 (30.5)
Low	8,336 (60.1)	5,248 (55.7)	3,566 (53.6)
High	481 (3.5)	661 (7.0)	1,059 (15.9)
ISABA (nebulizer)	2,017 (14.5)	575 (6.1)	571 (8.6)
Oral corticosteroid	2,547 (18.4)	2,250 (23.9)	2,121 (31.9)
Sodium cromoglycate	2,360 (17.0)	656 (7.0)	399 (6.0)
Nedocromil	116 (0.8)	116 (1.2)	123 (1.8)
Theophylline	294 (2.1)	1,789 (6.7)	1,659 (13.2)
Ipratropium and combination	397 (2.9)	480 (5.1)	813 (12.2)
Oral SABA	118 (0.9)	6 (0.6)	69 (1.3)
LABA	45 (0.3)	96 (1.0)	180 (2.7)
Leukotriene modifier	208 (1.5)	111 (1.2)	176 (1.5)
Combination therapy (corticosteroid and LABA)	23 (0.2)	33 (0.4)	41 (0.6)
Ketotifen	118 (0.9)	6 (0.1)	6 (0.1)

*Data are presented as No. (%).

follow-up time (2 years) for this cohort being within the median time to hospitalization (1.06 years). Subjects who had one or more average number of asthma-related physician visits per 3 months during the follow-up were 11.46 times more likely to be hospitalized in comparison to those who had one or fewer average number of visits per 3 months.

Univariate Analysis of Medication Use and Asthma Hospitalization

High use of ISABA administered by MDI and/or DPI and at least single use of ISABA administered by nebulizer, oral corticosteroids, theophylline, and ipratropium combinations were significant risk factors for asthma hospitalization in the univariate analysis (Table 4). Persons with low use of ISABA administered with MDI and/or DPI, low use of ICS, and at least single use of nedocromil, LABA, and leukotriene modifiers were less likely to be hospitalized for asthma (Table 4).

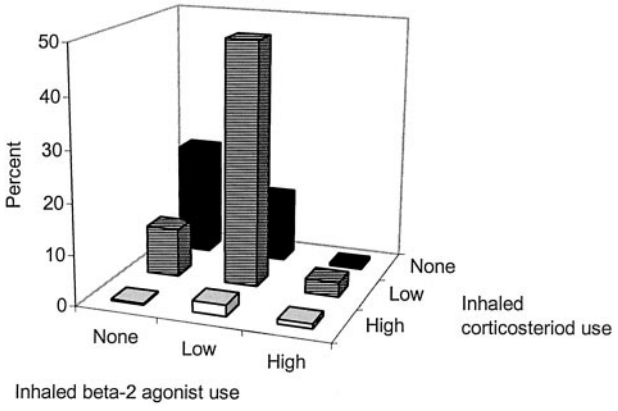

FIGURE 1. Cross-classification between average monthly use of inhaled SABA (MDI and DPI devices) and average monthly use of ICS use during the follow-up.

Multivariate Analysis of Medication Use and Asthma Hospitalization

The adjusted RRs of asthma hospitalization for medications that were significant risk factors in the Poisson regression analysis are given in Table 5. In the multivariate analysis, significant interactions were observed between use of ICS and use of ISABA administered by MDI and/or DPI. Risk of hospitalization for high use of ISABA decreased with increased use of ICS. In the absence of ICS use, high use of ISABA administered by MDI and/or DPI was associated with a fourfold increase in the risk of hospitalization for asthma. However, this risk reduced by 70% for low use of ICS, and there was a beneficial effect with 93% reduction in the rate of hospitalization for high use of ICS. Low use of ISABA administered by MDI and/or DPI showed an inverse association with asthma hospitalizations for all levels of ICS use, with the largest reduction in risk occurring at the high use of ICS. Use of oral corticosteroids and ISABA administered by nebulizer were associated with 30% and 38% increases in the rate of asthma hospitalizations, respectively. In the multivariate analysis, the average number of asthma-related physician visits per 3 months had the highest risk for asthma hospitalization (RR, 13.07; 95% CI, 11.76 to 14.52). In addition to the beneficial

Table 3—*Univariate RRs of Asthma Hospitalization for Demographic Factors*

Factors	Person-Years	Patients Hospitalized, No.	Rate per 1,000 per Year	RR (95% CI)
Age, yr				
35–54	31,788.7	544	17.11	1.00
15–34	45,962.8	660	14.36	0.84 (0.75–0.94)
5–14	67,915.5	982	14.46	0.85 (0.76–0.94)
Sex				
Female	66,599.0	1,145	17.19	1.00
Male	79,068.0	1,041	13.17	0.77 (0.70–0.83)
Entry period				
1991–1992	65,990.5	1,202	18.21	1.00
1993–1994	32,680.4	430	13.16	0.72 (0.65–0.81)
1995–1996	25,771.0	278	10.79	0.59 (0.52–0.68)
1997–1998	15,815.3	184	11.63	0.64 (0.55–0.75)
1999–2000	5,409.7	92	17.01	0.93 (0.76–1.15)
Residence				
Rural	60,673.3	984	16.22	1.00
Urban	84,993.7	1,202	14.14	0.87 (0.80–0.95)
Number of asthma-related physician visits per 3 mo				
≤ 1	138,401.7	1,365	9.86	1.00
> 1	7,265.2	821	113.00	11.46 (10.51–12.49)
Total	145,667.0	2,186	15.01	

effects of ICS use, beneficial effects were also observed for use of sodium cromoglycate (86% reduction in the rate of hospitalization), nedocromil (66% reduction), LABA (76% reduction), and leukotriene modifiers (86% reduction) and are presented in Table 5.

Controlling for Asthma Severity

The effect of asthma severity on the joint effect of ISABA and ICS was further assessed by conducting multivariate analysis in subgroups defined by users and nonusers of oral corticosteroid, users and nonusers of ISABA administered by nebulizer, and one or less and more than one asthma-related visits per 3 months to physicians during the follow-up (Table 6). The RR of hospitalization for high use of ISABA administered by MDI and/or DPI and no use of ICS was 2.16 among subjects with more than one asthma-related visits per 3 months to physicians and 10.06 among subjects with one or less asthma-related visit. However, the dose-response relationship between use of ISABA administered by MDI and/or DPI and use of ICS was still seen in the two groups, indicating that this relationship was independent of asthma severity. The change in the risk of hospitalization was smaller between users and nonusers of oral corticosteroids and between users and nonusers of ISABA administered by nebulizer in comparison to one or less and more than one asthma-related visit per 3 months (Table 6).

Discussion

This study was based on data from Saskatchewan Health databases for 10 years, from 1991 to 2000. These databases contain health-care utilization data of almost all of the total population of the Province of Saskatchewan, which receives universal health care and family based prescription drug coverage from the Government of Saskatchewan. Our study examined the effect of asthma medications in a cohort of persons with at least five asthma-related visits to a physician and did not have hospitalizations during the 2-year period prior to the start of cohort or during the waiting period prior to the entry into the cohort.

We found that low use of ISABA administered by MDI and/or DPI had an inverse association with asthma hospitalization for both ICS users and nonusers, but persons receiving high-dose ISABA administered by MDI and/or DPI without any use of ICS had a fourfold increase in the risk of asthma hospitalization. In the study conducted among children and adults using the HMO database in eastern Massachusetts, a fourfold increase in the risk of asthma hospitalization was reported for those dispensed eight or more ISABA prescriptions per person-year relative to those dispensed no ISABA prescriptions.[6] In a study[15] based on Kaiser Permanente HMO among adults with a mean age of 55 years, asthma subjects who received four or more canisters of ISABA during the 3-month period prior to the

Table 4—*Univariate RRs of Asthma Hospitalization for Use of Medications*

Factors	Person-Years	Patients Hospitalized, No.	Rate per 1,000 per Year	RR (95% CI)
ISABA (MDI and/or DPI)				
None	35,233.7	747	21.20	1.00
Low	103,389.2	1,105	10.69	0.50 (0.46–0.55)
High	7,044.0	334	47.42	2.24 (1.97–2.54)
ICS				
None	42,097.1	976	23.19	1.00
Low	93,935.4	981	10.44	0.45 (0.41–0.49)
High	9,634.5	229	23.77	1.03 (0.89–1.18)
ISABA (nebulizer)				
None	126,487.9	1,753	13.86	1.00
Yes	19,179.1	433	22.58	1.63 (1.47–1.81)
Oral corticosteroid				
No	105,573.0	1,370	12.98	1.00
Yes	40,094.0	816	20.35	1.57 (1.44–1.71)
Sodium cromoglycate				
No	121,587.8	1,810	14.89	1.00
Yes	24,079.2	376	15.62	1.05 (0.94–1.17)
Nedocromil				
No	143,357.9	2,172	15.15	1.00
Yes	2,309.1	14	6.06	0.40 (0.24–0.68)
Theophylline				
No	133,033.9	1,907	14.33	1.00
Yes	12,633.1	279	22.08	1.54 (1.36–1.75)
Ipratropium and combination				
No	135,846.8	1,996	14.69	1.00
Yes	9,820.2	190	19.35	1.32 (1.13–1.53)
Oral SABA				
No	135,718.7	2,036	15.00	1.00
Yes	9,948.3	150	15.08	1.01 (0.85–1.19)
LABA				
No	143,708.9	2,173	15.12	1.00
Yes	1,958.0	13	6.64	0.44 (0.25–0.76)
Leukotriene modifier				
No	144,724.3	2,177	15.21	1.00
Yes	942.6	9	3.59	0.24 (0.12–0.45)
Corticosteroid and LABA (combination therapy)				
No	145,161.7	2,186	15.06	1.00
Yes	505.3	0	0.00	0.00
Ketotifen				
No	143,162.5	2,173	15.01	1.00
Yes	2,504.4	13	13.79	0.92 (0.53–1.58)

hospitalization were 1.4 times more likely to be admitted to the ICU, and 1.9 times more likely to receive endotracheal intubations. In a study[23] conducted in Vancouver, Canada, among patients aged 5 to 50 years, inappropriate use of ISABA was associated with increased use of health-care resources associated with treatment of respiratory conditions.

The protective effect of ICS use on the risk of asthma hospitalization has been reported in several studies,[4–7,15] in which the reduction of asthma hospitalization rates associated with ICS use varied from 30 to 60%. In a nested case-control study using the Saskatchewan Health databases from 1975 to 1991, regular use of ICS was associated with a reduction of 31% in the asthma hospitalization rates.[8] Interestingly, in our study, low ICS use, in the absence of ISABA use, had a reduction of 66% in the asthma hospitalization rates. High ICS use, in the absence of ISABA use, had an increased risk for asthma hospitalization, but it was not statistically significant. This increased risk was seen only among those persons with increased asthma severity indicated by more than one asthma-related physician visits per 3 months, on average. High ICS use was also associated with increased risk for asthma hospitalization in a cross-sectional study of Ohio Medicaid patients aged 15 to 64 years.[16] The increased risk of hospitalization for high ICS use might be partially attributed to asthma severity as increasing dose of ICS, assuming asthma is well controlled, can been used as

Table 5—*Adjusted RRs of Asthma Hospitalization for Use of Medications From Multivariate Poisson Regression Model

Factors	RR (95% CI)
ISABA (MDI and/or DPI)	
None	
No ICS	1.00
Low ICS	0.34 (0.28–0.42)
High ICS	1.26 (0.80–1.99)
Low	
No ICS	0.64 (0.56–0.74)
Low ICS	0.79 (0.64–0.97)
High ICS	0.23 (0.14–0.37)
High	
No ICS	4.00 (3.13–5.11)
Low ICS	1.18 (0.91–1.54)
High ICS	0.28 (0.17–0.47)
ISABA (nebulizer)	
No	1.00
Yes	1.38 (1.23–1.56)
Oral corticosteroid	
No	1.00
Yes	1.30 (1.17–1.45)
Sodium cromoglycate	
No	1.00
Yes	0.14 (0.07–0.26)
Nedocromil	
No	1.00
Yes	0.34 (0.20–0.58)
LABA	
No	1.00
Yes	0.24 (0.14–0.41)
Leukotriene modifiers	
No	1.00
Yes	0.14 (0.07–0.26)

*In addition to the variables listed, age, sex, age × sex, entry period, residence, and average number of asthma-related physician visits per 3 months were included in the multivariate Poisson regression model.

an indicator of asthma severity.[32] Protective effects of ICS use have been reported for ED visits among children aged 3 to 15 years.[5] In a case-control study based on data from Saskatchewan Health databases for 1977 to 1993, asthma patients 5 to 54 years old treated with ICS in the year following the asthma diagnosis had a 40% reduction in asthma hospitalizations in comparison to those treated with theophylline.[13]

In our study, the risk of asthma hospitalization associated with high use of ISABA was reduced with increased average use of ICS, with a beneficial effect occurring when there was high use of ICS. In a study conducted using the HMO database in Eastern Massachusetts, ICS use was associated with a reduction in asthma hospitalization rates, and reduced the risk of asthma hospitalization associated with increased ISABA use.[6] The Massachusetts study included young children and old adults, and was based on a selective population with health and prescription drug coverage, while our study population included almost the whole population of Saskatchewan and excluded children aged < 5 years old and adults ≥ 55 years old due to concerns over comorbid conditions and accurate diagnosis of asthma. Drug use in the Massachusetts study was measured by dispensing rates, which was the ratio between the total number of prescriptions and the duration of follow-up[6]; in our study, average drug use was based on quantity and strength of drug dispensed by the duration of the follow-up period, which allowed us to categorize the average use of ISABA into low and high use according the asthma management guidelines. Findings similar to ours were observed in a study[12] examining the relationship between use of ISABA and asthma-related deaths. However, only the number of prescriptions and not the quantity dispensed was used to determine use of medications in this study.[12]

Researchers have investigated asthma severity as a possible reason for the association between use of SABA and asthma morbidity and mortality.[33,34] In these studies, previous hospitalizations,[33] use of oral corticosteroids,[34] a history of loss of consciousness or seizures during a previous asthma attack,[34] and a history of attacks of asthma precipitated by eating certain foods[35] were considered as markers of asthma severity. The latter two markers were associated with 10-fold and fivefold increased risk of near-fatal and fatal asthma, respectively.[34] In our study, the average number of asthma-related physician visits per 3 months during the follow-up was the most important marker of severity and was associated with more than a 10-fold increase risk of asthma hospitalization. The usage of oral corticosteroids and SABA administered by nebulizer was also considered to be markers of asthma severity in our study, but their effects were smaller than the average number of asthma-related physician visits per 3 months. Use of a nebulizer as an indicator of asthma severity is questionable, as the nebulizer is frequently used to administer β_2-agonists in very young children. However, this should not affect our study, as children < 5 years old were not included in our study. In addition, nebulizer use was significantly associated with increased asthma severity in a study[36] conducted among high-risk, inner-city adults ≥ 18 years old.

In our study, LABA and leukotriene modifiers were used only by a small proportion of the cohort, which might be related to the introduction of these drugs part-way through the study period in Canada. In addition, leukotriene modifiers were listed under the exception drug status in the Saskatchewan Drug Formulary.[27] Some of the dispensing of these drugs might not have been captured in the prescription

Table 6—*Joint Effect of ISABA and ICS in the Multivariate Analysis for High and Low Asthma Severity Groups*

Joint Effect	Dispensed Oral Corticosteroids During the Follow-up*		Dispensed ISABA for Nebulizer Administration During the Follow-up†		Average No. of Asthma-Related Physician Visits per 3 mo During the Follow-up‡	
	Yes RR (95% CI)	No RR (95% CI)	Yes RR (95% CI)	No RR (95% CI)	> 1 RR (95% CI)	≤ 1 RR (95% CI)
ISABA (MDI and/or DPI)						
None						
No ICS	1.00	1.00	1.00	1.00	1.00	1.00
Low ICS	0.58 (0.39–0.86)	0.26 (0.20–0.34)	0.65 (0.43–1.00)	0.25 (0.19–0.32)	0.42 (0.29–0.60)	0.30 (0.23–0.39)
High ICS	0.92 (0.45–1.89)	1.77 (0.96–3.27)	0.64 (0.22–1.88)	1.57 (0.94–2.62)	1.07 (0.63–1.88)	0.79 (0.29–2.11)
Low						
No ICS	0.70 (0.49–0.99)	0.63 (0.53–0.74)	0.81 (0.54–1.20)	0.61 (0.52–0.70)	1.35 (1.05–1.70)	0.46 (0.38–0.55)
Low ICS	0.46 (0.33–0.63)	0.96 (0.72–1.26)	0.34 (0.24–0.48)	1.10 (0.84–1.45)	0.46 (0.32–0.64)	0.92 (0.70–1.20)
High ICS	0.27 (0.13–0.55)	0.21 (0.11–0.40)	0.31 (0.11–0.91)	0.21 (0.12–0.35)	0.21 (0.12–0.35)	0.48 (0.17–1.33)
High						
No ICS	4.01 (2.47–6.53)	3.52 (2.62–4.72)	3.06 (1.18–7.93)	3.80 (2.95–4.92)	2.16 (1.51–2.95)	10.06 (6.99–14.47)
Low ICS	0.61 (0.42–0.91)	2.22 (1.55–3.18)	0.52 (0.32–0.84)	1.65 (1.19–2.29)	0.65 (0.42–0.93)	3.24 (2.29–4.59)
High ICS	0.42 (0.20–0.85)	0.19 (0.09–0.40)	0.56 (0.19–1.63)	0.21 (0.12–0.38)	0.23 (0.12–0.41)	1.10 (0.39–3.12)

*Adjusted for all the variables listed in Table 5 except oral corticosteroid, age, sex, age × sex, entry period, residence, and average number of asthma-related physician visits per 3 months using the multivariate Poisson regression model.

†Adjusted for all the variables listed in the Table 5 except ISABA administered by nebulizer, age, sex, age × sex, entry period, residence, and average number of asthma-related physician visits per 3 months using multivariate Poisson regression model.

‡Adjusted for all the variables listed in the Table 5, age, sex, age × sex, entry period, and residence using multivariate Poisson regression model.

drug databases and might have been excluded from the study. However, the main findings of our study will not be affected by this incomplete capture of the drugs under the exception drug status category, since most commonly used drugs involved in our findings were not part of that category.

There are several limitations in our study. One of the important assumptions in the study was that patients consumed all the drugs that they were dispensed, but it was not possible to verify this assumption. Use of oral corticosteroids, nebulizer-administered ISABA, and number of physician visits were used to control for asthma severity in our study, as no other direct indicators of severity were available. The information about ED visits during the follow-up was not available for our study, as it was not routinely captured in the Saskatchewan Health Databases. Aggressive management of asthma at the ED might have prevented hospitalizations. However, in a study conducted among children with acute asthma from 44 EDs in the United States and Canada, there was no significant difference in the mean number of past-year ED visits between those who were admitted to the hospital for asthma and those who were not admitted.[36] Only a small reduction is expected in the number of asthma-related physician visits due to ED visits because patients who were not compliant with the ED discharge guidelines would not have seen a physician following the ED visit. The ED discharge guidelines recommend that patients with asthma should see a physician within 1 week of discharge from the ED.[1,2]

In our study, low doses of ICS, and low doses of ISABA administered by MDI and/or DPI were associated with reductions in the rates of first hospitalization for asthma. In contrast, the risk of hospitalization was greater for high use of ISABA administered, which was progressively reduced by low and high use of ICS. We accounted for asthma severity by including three asthma severity indicators in the multivariate model and performed additional analyses stratified by severity indicators. Although the effects of severity could be seen, the patterns between ISABA, ICS, and hospitalization were still present and independent of severity. Our results support the current Canadian guidelines, which suggest regular ICS use with ISABA use as needed.[1,2] In the high-severity strata, high ISABA use without ICS use may indicate inappropriate management with overreliance on ISABA, thus resulting in hospitalization; whereas appropriate management, which includes ICS use, reduces the risk of hospitalization. Our study clearly showed this reduction in risk of asthma hospitalizations with the use of ICS. We conclude that use of more than one canister of ISABA per month represents inappropriate management and is an indicator for the use of ICS.

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