ORIGINAL ARTICLE

Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma

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Background: Inhaled corticosteroids are effective at preventing asthma morbidity and mortality. Most studies, however, have focused on short term effects, raising uncertainty about their effectiveness in the long term.

Methods: The Saskatchewan Health databases were used to form two population based cohorts of asthma patients aged 5–44 between 1975 and 1991. The first cohort included all subjects from the start of asthma treatment, while the second included subjects hospitalised for asthma from the date of discharge. Subjects were followed up, starting 1 year after cohort entry and continuing until 1997, 54 years of age, or death. The outcome was the first asthma hospital admission and readmission, respectively, to occur during follow up. A nested case-control design was used by which all cases were matched on calendar time and several markers of asthma severity to all available controls within the cohort.

Results: The full cohort included 30 569 asthmatic subjects of which 3894 were admitted to hospital for asthma and 1886 were readmitted. The overall rate of asthma hospitalisation was 42.4 per 1000 asthma patients per year. Regular use of inhaled corticosteroids was associated with reductions of 31% in the rate of hospital admissions for asthma (95% confidence interval (CI) 17 to 43) and 39% in the rate of readmission (95% CI 25 to 50). The rate reduction found during the first 4 years of follow up was sustained over the longer term. Regular use of inhaled corticosteroids can potentially prevent between five hospital admissions and 27 readmissions per 1000 asthma patients per year.

Conclusion: Regular use of low dose inhaled corticosteroids prevents a large proportion of hospital admissions with asthma, both early and later on in the course of the disease.

Inhaled corticosteroids are the treatment of choice in the management of asthma,[1–4] a common disorder whose prevalence is on the rise.[5–7] Their effectiveness in preventing major asthma related outcomes in the short term has been demonstrated in several epidemiological studies.[8 9] However, no study has evaluated the effects of inhaled corticosteroids on one of these major outcomes—namely, admission to hospital—over the long term.[8] This question is especially relevant because the rate of hospital admissions for asthma is high and has been increasing in frequency over the last decades in several countries including Canada and the United States.[6 10–16] The resources allocated to asthma hospitalisations, which totalled almost 1.8 billion dollars in 1997 in the US, also represent an important part of the total costs associated with asthma.[17–20] More importantly, this event is one of the most powerful predictors of asthma mortality[21–25] and of subsequent readmissions for asthma.[23 26]

Previous studies have shown that the preventive effect of inhaled corticosteroids on asthma hospital admissions was restricted to short term follow up.[27–29] The first of these studies included a median follow up of 1.5 years while the other two studies were both restricted to the first year of follow up after cohort entry. The second study showed that use of inhaled corticosteroids early in the disease course was very effective at preventing asthma hospitalisations during the first year of disease.[29] The third study, the only one that assessed this effect over time, found that the benefit appeared to fade with time.[28] In that 1 year cohort study of 2059 subjects admitted to hospital for asthma, subjects treated regularly with inhaled corticosteroids at discharge for up to 6 months were 40% less likely to be readmitted with asthma. However, this protective effect of inhaled corticosteroids seemed to disappear after 6 months of regular treatment (rate ratio 1.2). While the authors attributed this apparent loss of effectiveness to confounding, there is limited information on the benefit of inhaled corticosteroids over longer durations of disease and follow up.[30 31] In view of the lengthy duration of this disease, the question of whether the effectiveness of inhaled corticosteroids is sustained over the long term becomes of fundamental importance.

We have assessed whether the use of inhaled corticosteroids, particularly regular use, prevents asthma hospitalisation over the longer term in a large population based cohort. We studied the prevention of both the first hospital admission as well as subsequent readmission to hospital for asthma.

METHODS

Subjects and source of data

The cohort of asthmatic patients used as the source of data for this study has already been described in detail elsewhere.[9 28 29] Briefly, the cohort was formed using the computerised databases of Saskatchewan Health. These databases were developed as a result of the universal health insurance programme provided to all residents of this Canadian province since 1975. Two million people have been covered by the programme since 1975. The databases have been used extensively to study the effects of several prescription drugs at the population level.[32] We selected from this population all 30 569 beneficiaries aged 5–44 years who received at least three prescriptions of an anti-asthma medication in any 1 year period between September 1975 and December 1991. The medications included all anti-asthma medications, except for oral corticosteroids, covered by the health insurance plan during the study period—namely, beclomethasone, budesonide, triamcinolone acetate, flunisolide, sodium cromoglycate, ketotifen, nedocromil, salbutamol, fenoterol, terbutaline, isoproterenol, metaproterenol, procaterol, epinephrine

bitartrate, ipratropium bromide, and any compound of theophylline. Oral corticosteroids were not included to avoid selecting subjects with conditions other than asthma. However, all oral corticosteroid prescriptions were subsequently obtained for the selected subjects.

The subjects were followed from their first of three anti-asthma prescriptions until their 55th birthday, the date of death, the date of emigration from the province, the date of end of coverage of the health insurance plan, or 31 December 1997, whichever occurred first.

Study cohorts

Two study cohorts were formed from the source cohort. For each cohort we set the minimum duration of follow up at 1 year to be able to assess the effect of inhaled corticosteroids over the long term. Thus, for both cohorts only follow up and outcome events subsequent to the first year after cohort entry were considered. For each cohort that first year was taken as a 1 year baseline period.

The first cohort (that addresses this effect for all asthma patients) involved all subjects in the source cohort. Time zero for this cohort was 365 days after the date of entry into the source cohort, so that subjects observed for less than a year in the source cohort were excluded. This cohort therefore includes all subjects with at least 1 year follow up, irrespective of whether or not they were admitted to hospital for asthma during the baseline year. We refer to this cohort as the "full" cohort.

The second cohort (that addresses the effect on the risk of readmission for asthma) was formed from all subjects who had been admitted to hospital at least once during follow up of the source cohort. Time zero for this cohort (which we refer to as the "hospitalised" cohort) is thus 365 days after the date of discharge of the initial cohort defining hospital admission for asthma. Here again, this cohort includes all subjects with at least 1 year follow up after discharge (baseline), irrespective of whether or not they were admitted to hospital for asthma during this baseline year after a first hospital admission.

Outcome

For members of each cohort we identified the first asthma hospitalisation to occur after time zero—that is, after the 1 year baseline period. Asthma hospitalisation was defined as a primary discharge diagnosis of asthma (ICD-9 codes 493.0, 493.1, or 493.9). Cases occurring during or within a year of the period of June 1987 and December 1988 (18 months) were excluded since Saskatchewan Health did not collect medication data during this period.

Study design

We used a nested case-control design within each of the two cohorts to allow proper consideration of the time dependent nature of asthma drug use. Moreover, to control for confounding by indication, we also applied tight matching with respect to markers of asthma severity. Each hospital admission with asthma was matched to all available controls within the cohort on the basis of several factors. Firstly, to control for secular trends in inhaled corticosteroid use, the matched controls had the same calendar year and month of time zero as the case. Moreover, all matched controls had a duration of follow up at least as long as the time to asthma hospitalisation for the corresponding case, this date being designated the index date. Thus, in accordance with basic principles, a cohort member could be selected as a control more than once, albeit at different time points of their follow up.[33]

The following additional matching factors were used to control for disease severity as we expected the cases to be the more severe patients who may also be more likely to receive inhaled corticosteroids: the occurrence of asthma admissions to hospital during the 1 year baseline period (the year before time zero), the number of canisters of β agonists dispensed in the year before the index date (≤18, >18), the use of nebulised β agonists, theophylline, and oral corticosteroids, all in the year before the index date. For the few cases for which we could only find one or no controls, wider spans of the calendar month and year of cohort entry were used to identify more controls.

Inhaled corticosteroid exposure

We identified all prescriptions of inhaled corticosteroids that were dispensed to the cases and controls during the year before their index date. Each prescription was analysed to identify the number of canisters of inhaled corticosteroids dispensed concurrently. When two or more canisters were dispensed in the same prescription, the canisters were considered as if they had been dispensed in successive months. The 1 year time window of exposure before the index date was divided into 3 month quarters to quantify regularity of use.

Data analysis

Descriptive statistics used to compare the characteristics of cases and controls were based on weighted estimates for the controls because of the variable number of controls matching each case. They were weighted by the inverse of the number of controls in each matched set, which is equivalent to standardising the number of controls to one control per case.

Exposure to inhaled corticosteroids was quantified in different ways. We first determined the presence of any use during the year before the index date and then identified the timing at which the canisters were dispensed during this time period. To assess the effect of regular use of inhaled corticosteroids we divided the users into two strata defined in the 1 year time window: (1) regular use was defined as the dispensation of at least one canister of inhaled corticosteroids during each of the four quarters preceding the index date; (2) irregular use was defined as any other pattern of use during the four quarters preceding the index date.

Conditional logistic regression for matched case-control data was used to estimate adjusted rate ratios of asthma hospitalisation associated with the various patterns of inhaled corticosteroid use. In particular, regular users of inhaled corticosteroids were first compared with irregular users and non-users separately, as well as combined to form the reference group. To control for any residual confounding, in spite of matching on the presence or absence of the severity measures, we adjusted all rate ratio estimates for the quantities of prescribed drugs used in matching—namely, the number of dispensed prescriptions of theophylline, nebulised and oral β agonists, oral corticosteroids, as well as the number of canisters of inhaled β agonists dispensed in the year before the index date. We also adjusted for the number of hospital admissions for asthma during the year before cohort entry, as well as age and sex.

RESULTS

The source cohort included 30 569 asthmatic subjects who were followed for 346 340 person-years during which a total of 16 609 hospital admissions for asthma occurred, giving an overall rate of 48.0 asthma hospital admissions per 1000 asthma patients per year. The full cohort, formed during the follow up of the source cohort that started after the 1 year baseline period, comprised 4673 patients who were admitted to hospital for asthma, of which 3894 admissions occurred during the period when data were available. These 3894 hospitalised cases were matched to 35 399 controls selected from the cohort follow up time. In this full cohort the overall rate of asthma hospitalisation was 42.4 per 1000 asthma patients per year, while the rate of a first asthma hospitalisation was 17.2 per 1000 patients per year.

Table 1 Characteristics of cases and controls from the full and hospitalised cohorts

	Full cohort		Hospitalised cohort	
	Cases	Controls*	Cases	Controls*
Number	3894	35399	1886	13636
Mean age (years)	20.4	23.2	21.8	23.0
Percentage male	50.9	55.9	48.8	51.1
Asthma hospital admissions during baseline (mean)	0.39	0.31	0.78	0.68
Frequency of matching asthma drugs during the year before the index date (mean)				
Oral corticosteroid prescriptions	0.60	0.57	0.98	0.76
Inhaled β agonist metered dose inhalers	6.88	5.16	9.24	7.12
Nebulised β agonist prescriptions	0.50	0.45	0.77	0.56
Oral β agonist prescriptions	1.30	0.92	0.95	0.72
Theophylline prescriptions	1.92	1.87	2.13	1.94

*To account for case-control matching, all means and percentages for controls are weighted by the inverse of the number of controls in each case-control matched set.

Table 2 Characteristics of users and non-users of inhaled corticosteroids among the 35 399 controls from the full cohort and the 13 636 controls from the hospitalised cohort

	Full cohort			Hospitalised cohort		
	Regular use	Irregular use	Non-use	Regular use	Irregular use	Non-use
Number	1351	6566	27482	1021	3703	8912
Proportion (%)	3.8	18.6	77.6	7.5	27.2	65.3
Mean age (years)	29.1	24.8	22.3	29.2	24.4	21.2
Percentage male	56.7	52.8	56.7	49.6	48.3	52.8
Time to index date (years)	5.1	4.4	4.2	4.6	4.4	4.5
Hospitalisation during baseline (%)	33.8	29.5	21.3	50.6	46.9	37.8
Medication use in the previous year (%):						
Oral corticosteroids	48.1	37.2	10.6	41.2	37.9	11.2
Inhaled β agonists (>18 MDIs)	21.2	12.1	6.0	20.6	11.4	8.0
Nebulised β agonists	14.9	18.5	7.3	21.8	23.1	8.8
Theophylline	50.4	40.7	36.1	45.0	36.7	34.3

MDI=metered dose inhaler.

The hospitalisation cohort was formed by the subset of 5894 asthmatic patients with at least one hospital admission for asthma who were followed for 54 155 person-years after the 1 year baseline. Of the 2283 who were subsequently readmitted to hospital for asthma after a 1 year baseline period, 1886 occurred during the period when data were available and were matched to 13 636 controls selected within this cohort. The overall rate of readmission for asthma in this cohort was 153.4 per 1000 asthma patients per year, while it was 68.8 for the first readmission.

Among the cases and matched controls from the full cohort, 23.6% were admitted to hospital for asthma in the year before cohort entry, 17.8% were dispensed oral corticosteroids, 6.7% received more than 18 canisters of inhaled β agonists, 9.9% were given nebulised β agonists, and 37.7% theophylline. Asthma was more severe among the cases and matched controls from the hospitalised cohort, as 41.8% had been admitted to hospital for asthma during the 1 year baseline period while, during the year before the index date, 22.1% were dispensed oral corticosteroids, 9.2% received more than 18 canisters of inhaled β agonists, 13.2% were given nebulised β agonists, and 37.4% received theophylline. The mean duration of follow up was 10.8 and 7.6 years, respectively, for the full and readmitted cohorts.

Table 1 shows the frequencies of the matching characteristics for the cases and controls in each of the two cohorts. Despite matching on their presence or absence, the actual numbers of prescriptions and hospital admissions were slightly greater for the cases than the controls, indicating possible residual confounding that justifies further adjustment in the analyses.

Table 2 shows the characteristics of control patients from the two cohorts according to the use of inhaled corticosteroids during the year before the index date. In the full cohort only 22.3% of control patients had been dispensed inhaled corticosteroids at least once in the year before the index date compared with 34.7% in the hospitalised cohort. This table indicates that non-users of inhaled corticosteroids have much milder asthma than users. On the other hand, regular and irregular users are more homogeneous with respect to these markers of asthma severity. The majority (93%) of inhaled corticosteroid canisters identified during the 1 year time window were low dose beclomethasone (200 puffs at 50 µg per puff or the equivalent dry powder formulation).

Table 3 presents the crude (matched) and adjusted matched rate ratios of asthma hospitalisation for the various patterns of inhaled corticosteroid use during the 12 month time window before the index date. For the full cohort, using regular use as the reference, the adjusted rate ratio for irregular use during this period was 1.73 (95% confidence interval (CI) 1.41 to 2.11), while for non-use it was 1.28 (95% CI 1.05 to 1.56). For the hospitalised cohort the corresponding adjusted rate ratios were 1.69 (95% CI 1.36 to 2.01) and 1.59 (95% CI 1.28 to 1.94).

Table 4 presents the adjusted rate ratios of asthma hospitalisation for regular use, combining irregular and non-use as the reference, and stratifying by the duration of follow up. For the full cohort regular use of inhaled corticosteroids leads to a 31% (95% CI 17 to 43) reduction in the rate of hospital admissions for asthma. This rate reduction is equivalent in the first 4 years of follow up and subsequently. For the hospitalised cohort the rate reduction associated with regular use was 39% (95% CI 25 to 50) and was also constant over the follow up period. In view of these consistencies, we can estimate the overall impact of regular inhaled corticosteroid use in both cohorts combined as a rate reduction of 34% (95% CI 24 to 42), which is also very stable over time.

Table 3 Crude and adjusted rate ratios of asthma hospitalisation for patterns of inhaled corticosteroid use during the year before the index date for the full and hospitalised cohorts

Inhaled corticosteroid use during the 1 year period before the index date	Cases	Controls	Crude rate ratio	Adjusted* rate ratio (95% CI)
Full cohort				
Number of subjects	3894	35399		
Regular use (%)	3.6	3.8	1.00	Reference
Irregular use (%)	26.9	18.6	1.66	1.73 (1.41 to 2.11)
Non use (%)	69.5	77.6	1.09	1.28 (1.05 to 1.56)
Hospitalised cohort				
Number of subjects	1886	13636		
Regular use (%)	6.8	7.5	1.00	Reference
Irregular use (%)	35.0	27.2	1.65	1.69 (1.36 to 2.01)
Non use (%)	58.2	65.3	1.35	1.59 (1.28 to 1.94)

*In addition to matching, rate ratios are further adjusted for the number of dispensed prescriptions of theophylline, nebulised and oral β agonists, oral corticosteroids, and the number of canisters of inhaled β agonists, all dispensed during the year before the index date, as well as the number of asthma hospitalisations during the year before cohort entry, age, and sex.

Table 4 Adjusted rate ratios and rate reductions of asthma hospitalisation for regular inhaled corticosteroid use relative to both irregular and non-use during the year before the index date, according to follow up time, for the full and hospitalised cohorts

	Cases	Controls	Adjusted* rate ratio (95% CI)	Rate reduction (%)
Full cohort				
Follow up: overall	3894	35399	0.69 (0.57 to 0.83)	31%
<4 years	2388	22080	0.70 (0.54 to 0.92)	30%
>4 years	1506	13319	0.65 (0.49 to 0.89)	35%
Hospitalised cohort				
Follow up: overall	1886	13636	0.61 (0.50 to 0.75)	39%
<4 years	1052	7879	0.58 (0.43 to 0.77)	42%
>4 years	834	5757	0.65 (0.48 to 0.89)	35%
*Combined cohorts***				
Follow up: overall	5780	49035	0.66 (0.58 to 0.76)	34%
<4 years	3440	29949	0.65 (0.53 to 0.79)	35%
>4 years	2340	19086	0.66 (0.54 to 0.81)	34%

*In addition to matching, rate ratios are further adjusted for the number of dispensed prescriptions of theophylline, nebulised and oral β agonists, oral corticosteroids and the number of canisters of inhaled β agonists, all dispensed during the year before the index date, as well as the number of asthma hospitalisations during the year before cohort entry, age, and sex.
**Combining the full and hospitalised cohort.

DISCUSSION

In this large scale population based study we found that, over the long term, regular use of inhaled corticosteroids is associated with a reduction in the rate of hospital admissions for asthma of one third. This reduction was more pronounced in the more severe cohort limited to patients previously hospitalised for asthma and who are at greatest risk of being readmitted. The effect was sustained even after 4 years of follow up, indicating effectiveness early and further on in the course of the disease.

This study highlights the need to focus on regular use of inhaled corticosteroids in assessing their effectiveness in preventing major asthma outcomes. This observation was previously made in a study of the effectiveness of inhaled corticosteroids in preventing asthma death[9] and their short term effectiveness in preventing asthma hospital admissions.[28 29] The former study[28] found that the benefit of regular use appeared to fade with time, a finding the authors attributed to confounding. The reference group used comprised patients who were not dispensed inhaled steroids for up to a year after discharge from the initial hospital admission. That group of patients was shown to be clearly different in terms of asthma severity from patients who were dispensed these drugs, so the comparison was confounded. We also found in our study that non-users of inhaled corticosteroids had substantially milder asthma than users, albeit more so in the full cohort than in the hospitalised cohort. Despite this, regular use was found to be effective relative to either irregular or non-users. It is noteworthy that the pattern of regular or irregular use was defined exclusively during the year before the index date, irrespective of the usage patterns before that year. Whether these previous patterns have a bearing on the effectiveness could be the object of future research.

A potential bias from this type of study is confounding induced by the lack of random allocation of patients to treatment with inhaled corticosteroids. Such bias is expected as patients with more severe asthma, who have a higher rate of asthma hospitalisation, are more likely to be prescribed and dispensed inhaled corticosteroids. Thus, without proper statistical control, inhaled corticosteroids will appear to be ineffective at preventing this outcome. Our study was therefore designed to avoid this bias by matching cases and controls with respect to markers of asthma severity. Despite such tight matching, the cases still appeared to have slightly

more severe asthma than the controls and regression analysis was required to control for this residual confounding. Some confounding by indication may remain, however, and will usually result in an underestimation of the true benefit of inhaled corticosteroids. We can therefore deduce that the true benefit of inhaled corticosteroids is, in fact, greater than that found. An alternative explanation for these findings is the possibility that regular use of inhaled corticosteroids is simply a proxy for good asthma management, and that irregular use reflects poor management. Indeed, patients taking inhaled corticosteroids regularly appear to be better managed and more compliant with treatment.[34] However, we found that regular inhaled corticosteroid use is also more effective than no use, despite the wide disparity in the asthma severity of these two groups and the resulting confounding. Irrespective of causality arguments, the findings of our study establish that regular use of inhaled corticosteroids is an integral component of an effective asthma management programme.

The implications of our results for the treatment of asthma are important. This study strongly suggests that it is not the use—but the regular use—of inhaled corticosteroids that is essential to the effectiveness of these drugs. In addition, this effectiveness is sustained in the long term as long as the medications are taken regularly. This aspect of asthma management seems especially important in view of suggestions that compliance with inhaled corticosteroids appears to diminish over time on treatment.[35] Our study indicates that few patients were actually benefiting from these medications. In our full cohort 22.3% of subjects had been dispensed inhaled corticosteroids sometime during the year before the index date but only 3.8% used them regularly, while in the hospitalised cohort 34.7% were prescribed inhaled corticosteroids but only 7.5% used them regularly. Thus, only 15–20% of users deemed to need these drugs use them regularly and draw the full benefit. Recognising that this study spanned the period 1976–97 when the primary role of inhaled corticosteroids was less emphasised, it nevertheless seems important to assess and monitor these patterns of use. In addition, strategies such as targeting of patients at greatest risk for exacerbations, patient education on the importance of regular treatment, and reassurance concerning safety could help to ensure that the potential benefits suggested by clinical trials and observational studies can be translated into benefits at the clinical and population level.[36]

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