

First treatment with inhaled corticosteroids and the prevention of admissions to hospital for asthma

Lucie Blais, Samy Suissa, Jean-François Boivin, Pierre Ernst

Abstract

Background—Early treatment with inhaled corticosteroids appears to improve clinical symptoms in asthma. Whether a first treatment initiated in the year following the recognition of asthma can prevent major outcomes such as admission to hospital has yet to be studied.

Methods—A case-control study nested within a cohort of 13 563 newly treated asthmatic subjects selected from the databases of Saskatchewan Health (1977–1993) was undertaken to investigate the effectiveness of a first treatment with inhaled corticosteroids in preventing admissions to hospital for asthma. Study subjects were aged between five and 44 years at cohort entry. First time users of inhaled corticosteroids were compared with first time users of theophylline for a maximum of 12 months of treatment. The two treatments under study were further classified into initial and subsequent therapy to minimise selection bias and confounding by indication. Odds ratios associated with hospital admissions for asthma were estimated using conditional logistic regression. Markers of asthma severity, as well as age and sex, were considered as potential confounders.

Results—Three hundred and three patients admitted to hospital with asthma were identified and 2636 matched controls were selected. Subjects initially treated with regular inhaled corticosteroids were 40% less likely to be admitted to hospital for asthma than regular users of theophylline (odds ratio 0.6; 95% CI 0.4 to 1.0). The odds ratio decreased to 0.2 (95% CI 0.1 to 0.5) when inhaled corticosteroids and theophylline were given subsequently.

Conclusion—The first regular treatment with inhaled corticosteroids initiated in the year following the recognition of asthma can reduce the risk of admission to hospital for asthma by up to 80% compared with regular treatment with theophylline. This is probably due, at least in part, to reducing the likelihood of a worsening in the severity of asthma.

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of treatment with inhaled corticosteroids nearer to the onset of symptoms has been proposed.^{1,2} Two small randomised clinical trials have reported that initiation of regular treatment with inhaled corticosteroids early in the course of disease was more efficacious than regular treatment with terbutaline, a β agonist, in improving the clinical status of asthmatic subjects and in reducing the level of bronchial inflammation.^{2,3} However, early and long term treatment with inhaled corticosteroids remains controversial because of concerns regarding the frequency and severity of side effects.^{4–6} The potential of treatment with inhaled corticosteroids, initiated early after the recognition of asthma, to prevent major events such as admission to hospital—which heralds the presence of more severe, uncontrolled or deteriorating asthma—has yet to be studied.

Non-experimental studies provide the opportunity to assess the potential of a medication to prevent infrequent but serious events such as admission to hospital for asthma in the context of usual clinical practice.^{7–10} In this study we have used a cohort of newly treated asthmatic subjects to assess the potential of the first treatment with inhaled corticosteroids, initiated in the year following the recognition of asthma, in preventing the first hospital admission for asthma.

Methods

The computerised health insurance databases of Saskatchewan, a Canadian province of one million inhabitants, were used to select a cohort of newly treated asthmatic subjects. The provincial health insurance plan covers approximately 95% of the residents of that province and the databases contain information since 1975 on health services provided to the beneficiaries of this insurance plan, including medications dispensed and admissions to hospital.¹¹ During the study period the beneficiaries were admitted to hospital at no charge but they had to pay a portion of the cost of their prescribed medications, except for those receiving social assistance who were entitled to receive all formulary drugs at no charge. From 1977 to 1988 the beneficiaries had to pay a maximum of \$3.95 per dispensed prescription and from 1989 to 1993 they had to pay 20% of the cost of the medications after reaching a deductible of \$125 per family per year.

COHORT SELECTION

Cohort members were beneficiaries of the Saskatchewan Health Plan aged between five and 44 years who were dispensed, from 1977 to

Division of Clinical Epidemiology, Department of Medicine, Royal Victoria Hospital, Department of Medicine, Jewish General Hospital, Department of Medicine, Montreal General Hospital, and Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada
L Blais
S Suissa
J-F Boivin
P Ernst

Correspondence to:
Dr L Blais, Centre de recherche du CHUM, Campus Hôtel-Dieu, 3850 Saint-Urbain, Room 8–223, Montreal, Quebec, Canada H2W 1T8.

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Since the recognition that airway inflammation is present even in mild asthma, early initiation

1991, at least three prescriptions of an anti-asthma medication in the year following the first prescription recorded in the database. The prescription database was created in September 1975 but entry into the cohort was restricted to the 14 933 subjects who fulfilled the entry criteria after 31 August 1977 in order to ensure that cohort members had not been dispensed any prescription for asthma for at least two years before entry into the cohort. The medications considered for the selection of cohort members were all anti-asthma medications covered by the health insurance plan during the study period: the inhaled corticosteroids beclomethasone, budesonide, triamcinolone acetate and flunisolide; oral corticosteroids; anti-allergic agents such as sodium cromoglycate and nedocromil; β agonist bronchodilators such as salbutamol (albuterol in the USA), fenoterol, terbutaline, isoproterenol, metaproterenol, procaterol, epinephrine bitartrate; and ipratropium bromide, ketotifen and any derivative of theophylline.

Between 1 July 1987 and 31 December 1988 Saskatchewan Health stopped, for administrative reasons, recording the dispensed prescriptions on an individual basis.¹¹ No information was therefore available for the prescriptions dispensed during that period. To ensure that cohort members were only newly treated asthmatics, we eliminated 1370 subjects (out of 14 933) who had their first recorded prescription for asthma between 1 January 1989 and 30 June 1989. With this strategy, the 1139 subjects who entered the cohort between 1 July 1989 and 31 December 1990 had not been dispensed any prescription for asthma for a minimum of six months preceding cohort entry compared with the two year period applied to the majority of the cohort members.

The cohort thus comprised 13 563 newly treated asthmatic subjects followed from the date of their first anti-asthma prescription dispensed on or after their fifth birthday until the first of the following events: the date of their 55th birthday; death; emigration from the province; the end of coverage by the health insurance; 30 June 1987 (subjects entering the cohort before that date were censored on 30 June 1987 since dispensed prescriptions were

not available between 1 July 1987 and 31 December 1988); or 31 December 1993. Strictly speaking, follow up should have begun on the date of the third dispensed prescription for asthma rather than the first prescription since this third prescription represented the defining event for entry into the cohort. However, subjects were followed from the first prescription to ensure that they were in the cohort when treatment with inhaled corticosteroids was initiated; in a large number of early users of inhaled corticosteroids their treatment was initiated before the date of the third dispensed prescription for asthma. The potential bias induced by our use of the first prescription date will be discussed further below. Through linkage of the cohort with the hospital database we identified all subjects who were admitted to hospital with asthma during the study period.

OUTCOME DEFINITION

The outcome was the first admission to hospital for asthma to occur after entry into the cohort. We retained hospital admissions with a primary discharge diagnosis of asthma (ICD-9 codes 493.0, 493.1, or 493.9) and those with a secondary discharge diagnosis of asthma and a primary discharge diagnosis that was either an alternative code for asthma such as bronchitis, a precipitating factor of asthma such as upper respiratory tract infection, or a complication of asthma such as pneumothorax (ICD-9 codes 426.4, 427.0, 427.1, 427.3, 427.5, 427.8, 427.9, 460, 461.9, 462, 463, 464.2–465.9, 466.0, 466.1, 472.0, 472.2, 476.0 to 478.9, 487.0, 487.1, 487.8, 490, 491.2, 491.9, 492, 494, 496, 508.0, 508.8, 512, 516.8, 518.0 to 519.9, or 786.0–786.6).

CONTRASTED TREATMENTS

Two exposure contrasts were studied. Firstly, first time regular users of inhaled corticosteroids were compared with first time regular users of theophylline. Both treatments had been initiated in the year following the receipt of the first ambulatory treatment for asthma. Theophylline was selected as the reference in order to provide a reference group which was of comparable disease severity to the group of patients treated with inhaled corticosteroids. Theophylline, like inhaled corticosteroids, was prescribed in the 1980s principally to patients with moderate to severe asthma uncontrolled with β agonists alone.¹² Regular use of either inhaled corticosteroids or theophylline was defined as the dispensing of the medication at a rate of at least one prescription every three months. Secondly, irregular use of inhaled corticosteroids (a rate less than one prescription every three months) was contrasted with regular use of theophylline. For both contrasts we focused on the effectiveness of inhaled corticosteroids during the first 12 months of treatment.

NESTED CASE-CONTROL ANALYSIS

We conducted a case-control analysis nested within the cohort. All first admissions to hospital for asthma occurring within the first 12 months of treatment with inhaled cortico-

Table 1 Selected characteristics of study subjects and exposure to study medications

Characteristics	Cases (n = 303)	Controls (n = 2636)
Age at treatment initiation (%)		
5–14	48.5	41.1
15–20	15.2	18.0
21–54	36.3	40.9
% Male	45.2	48.8
Hospital admissions for asthma before cohort entry (%)	1.3	0.6
Study therapies (no. of subjects)		
Inhaled corticosteroids:		
Regular	47	658
Irregular	17	273
Theophylline: Regular	239	1705
Medications dispensed in the 6 months prior to treatment initiation (%)		
β agonists		
Inhaled (>1.5 prescriptions/month)	22.8	28.7
Oral	20.8	14.7
Nebulised	1.3	1.2
Oral corticosteroids	4.0	3.6
Ipratropium bromide	0.3	0.7

Table 2 Distribution of controls by potential confounders according to regular use of inhaled corticosteroids or theophylline

Confounders	Initial therapy (%)		Subsequent therapy (%)	
	Inhaled corticosteroids (n = 433)	Theophylline (n = 1507)	Inhaled corticosteroids (n = 225)	Theophylline (n = 198)
Medications dispensed in the 6 months prior to treatment initiation:				
β agonists:				
Inhaled (>1.5 prescriptions/month)	49.7	16.1	40.4	45.5
Oral	6.0	9.5	35.6	45.0
Nebulised	0.7	0.4	3.1	6.1
Oral corticosteroids	0.7	1.1	16.0	11.1
Ipratropium bromide	0.0	0.1	4.0	3.5
Age at treatment initiation:				
Less than 15 years	36.3	46.4	33.8	31.3
Hospital admission for asthma before cohort entry				
	0.2	0.8	0.0	0.5

steroids or theophylline (not both) were identified. We then selected a maximum of 10 matched controls per case using density sampling.¹³ Matching was done so that cases and controls had the same duration of disease (± 3 months) when the contrasted treatments were initiated—that is, the time between the first ambulatory treatment for asthma and initiation of treatment with either inhaled corticosteroids or theophylline—and the same duration of treatment at the index date (date of admission to hospital for cases and the corresponding matched date for controls). Matching was also done on the calendar year of entry into the cohort to control for secular trends in medical practice. Moreover, to be included in the case-control analysis, subjects should not have been prescribed any other anti-inflammatory agents (sodium cromoglycate or nedocromil) before the index date.

The two treatments under study were classified as either regular or irregular and were further classified as initial therapy if the treatment was initiated before the third dispensed prescription for asthma and as subsequent therapy if initiated at or after the third prescription. In both cases, however, the contrasted therapies were initiated in the year following the receipt of the first ambulatory treatment for asthma.

The odds ratios for the first hospital admission for asthma were estimated using two conditional logistic regression models: one model contrasting regular use of inhaled corticosteroids and theophylline, and a second model contrasting irregular use of inhaled corticosteroids with regular use of theophylline. The following covariates were treated as potential confounders: dispensing in the six months preceding the initiation of the treatment under study of 1.5 prescriptions or more

of inhaled β agonists per month, at least one prescription of oral β agonists, β agonists by nebulisation, oral corticosteroids or ipratropium bromide. Age of the subject at the initiation of treatment, sex, and whether a subject had been admitted to hospital for asthma before the receipt of the first ambulatory treatment for asthma were also considered as potential confounders. Moreover, we tested whether the timing of the treatment (either initial or subsequent) affected the effectiveness of inhaled corticosteroids. The most parsimonious models were selected using a backward elimination strategy.¹⁴

Results

We identified 303 first admissions to hospital for asthma and 2–10 controls per case were selected giving a total of 2636 controls. Table 1 gives the distribution of the study subjects by selected characteristics, study medications, and potential confounders. Only a few subjects, 1.3% of the cases and less than 1% of the controls, had been admitted to hospital for asthma before receiving their first ambulatory treatment for asthma; 16% of cases and 25% of controls had been treated regularly with inhaled corticosteroids before their index date.

Table 2 shows the distribution of potential confounders according to regular use of inhaled corticosteroids or theophylline among controls. Initial users of inhaled corticosteroids were more likely than users of theophylline to use more than 1.5 canisters of inhaled β agonists per month. When the treatments were given subsequently, users of inhaled corticosteroids were more likely to use oral corticosteroids than users of theophylline but less likely to use oral and nebulised β agonists and to be admitted to hospital for asthma before

Table 3 Effect of the first 12 months of early treatment with inhaled corticosteroids (initiated in the year following the first ambulatory treatment for asthma) in reducing the risk of admission to hospital for asthma

Compared therapies	Initial therapy				Subsequent therapy			
	Cases	Controls	Odds ratios		Cases	Controls	Odds ratios	
			Crude	Adjusted (95% CI)			Crude	Adjusted (95% CI)
Use of inhaled corticosteroids								
Regular	32	433	0.6	0.6* (0.4 to 1.0)	15	225	0.2	0.2* (0.1 to 0.5)
Irregular	8	150	0.9	0.9† (0.3 to 2.7)	9	123	1.0	1.0† (0.3 to 3.7)
Regular use of theophylline	199	1507	Reference		40	198	Reference	

*The odds ratios for regular treatment with inhaled corticosteroids, initial or subsequent, were estimated using a conditional logistic regression model and adjusted for age at the initiation of treatment and sex. Regular treatment with theophylline was used as the reference category.

†The odds ratios for irregular treatment with inhaled corticosteroids, initial or subsequent, were estimated using a conditional logistic regression model and adjusted for age at the initiation of treatment. Regular treatment with theophylline was used as the reference category.

receiving the first ambulatory treatment for asthma.

Table 3 summarises the results of the regression analyses. During the first year of treatment subjects initially treated with inhaled corticosteroids were 40% less likely to be admitted to hospital for asthma than regular users of theophylline, with an adjusted odds ratio (OR) of 0.6 (95% CI 0.4 to 1.0). When the contrasted therapies were given subsequently, the OR decreased to 0.2 (95% CI 0.1 to 0.5). Apart from the compared therapies, only age and sex were kept in the final model; all other variables considered for adjustment were not found to be confounders. Irregular users of inhaled corticosteroids did not appear to be protected against the first admission to hospital for asthma.

Discussion

We found that the first regular treatment with inhaled corticosteroids considerably reduced the risk of being admitted to hospital for asthma during the first 12 months of treatment. Regular users of inhaled corticosteroids were either 40% (initial therapy) or 80% (subsequent therapy) less likely than regular users of theophylline to be admitted to hospital for asthma. No such reduction in the risk of admission to hospital was found for irregular users of inhaled corticosteroids, even if this treatment was given at an early stage.

Admission to hospital for asthma is a well recognised marker of severe asthma or uncontrolled disease as indicated by an increased risk of a subsequent fatal attack.¹⁵⁻¹⁸ Treatment with inhaled corticosteroids initiated within the year of the recognition of asthma may therefore prevent aggravation of the disease that leads to more severe and chronic asthma and also reduce the cost of hospital admissions for asthma in Canada and in the USA which represents, respectively, 28% and 24% of the total costs for asthma.¹⁹⁻²⁰

Five published studies have investigated the potential clinical benefit of early treatment with inhaled corticosteroids but none considered the impact on a major outcome such as admission to hospital. In a randomised clinical trial of 103 recently diagnosed asthmatic subjects Haahtela *et al* found that budesonide was more effective in improving peak expiratory flow rate and in reducing bronchial responsiveness and symptoms of asthma than terbutaline over a two year period.³ In a randomised clinical trial using bronchial biopsy specimens Laitinen *et al*² showed that the number of inflammatory cells was reduced in all seven patients using inhaled corticosteroids after three months of treatment, while in four of the seven patients treated with terbutaline the number of inflammatory cells had increased. In three non-experimental studies it was reported that the improvement in lung function of subjects receiving inhaled corticosteroids was inversely proportional to the duration of symptoms prior to the initiation of therapy.²¹⁻²³ These results were, however, obtained from non-randomised studies in which the role of confounding by

asthma severity at the initiation of the treatment with inhaled corticosteroids was not adequately addressed.

Our results are based entirely on data from computerised prescription files of dispensed medications; this may not coincide precisely with actual intake of these medications. On the other hand, by using computerised databases the potential for recall bias of drug exposure was eliminated. Based on the minimal dose recommendation for the treatment of moderate to severe asthma with inhaled corticosteroids,¹⁵ we assumed that every prescription of inhaled corticosteroids or theophylline lasted up to three months. The assumption that each prescription is worth three months, which is rather long, would have the effect, if any, of underestimating the true beneficial effect of treatment.

Confounding by indication will be present if the allocation of the medications under study is associated with prognostic factors such as disease severity. This bias can probably explain, at least in part, the difference observed between the odds ratios associated with initial and subsequent regular therapies. The odds ratio for subsequent therapy is likely to be less confounded by indication since the contrasted medications were initiated when the treating physician felt the need for either a change in medication or the addition of a new medication.

Another possible explanation for the difference between initial and subsequent therapy is selection bias due to the fact that some subjects initially treated with the medications under study were admitted to hospital for asthma before they reached the criterion used for cohort selection—that is, three or more prescriptions for asthma. Selection bias would thus be present if subjects initially treated with inhaled corticosteroids were more likely to be controlled with their therapy than subjects initially treated with theophylline, leaving only users of inhaled corticosteroids suffering from more severe asthma, and therefore more likely to be admitted to hospital, meeting the selection criteria for entry into the cohort. This explanation is plausible since inhaled corticosteroids are known to reduce the need for β agonists.^{3,24} Under this selection process the odds ratio that we estimated for initial therapy (0.6) would represent an underestimation of the potential of inhaled corticosteroids to prevent admission to hospital for asthma. The odds ratio associated with regular use of inhaled corticosteroids given as subsequent therapy is free from this selection bias since the hospital admissions implied in this estimate occurred after the cohort selection criterion—that is, the third prescription.

On the other hand, not controlling for the area of residence of the subjects—which may well correlate with the number of hospital beds available per inhabitant—may have overestimated the beneficial effect of inhaled corticosteroids. However, area of residence classified as rural versus urban was not found to be a confounder in a previous study conducted in Saskatchewan on the relationship between

inhaled corticosteroids and the risk of death and near death from asthma.²⁵

Irregular users of inhaled corticosteroids, regardless of whether the medication was given as initial or as subsequent therapy, did not benefit from a reduction in the risk of hospital admission for asthma. This result suggests that inhaled corticosteroids need to be taken regularly, as recommended in the current guidelines, to obtain their beneficial effect.^{12 15 26 27}

In conclusion, we have shown that the first regular treatment with inhaled corticosteroids can reduce, by up to 80%, the risk of being admitted to hospital for asthma during the first year of treatment compared with regular treatment with theophylline. This is probably due, at least in part, to a reduction in the likelihood of a worsening in the severity of asthma.

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