Inhaled corticosteroids and the risk of diabetes among the elderly

Nandini Dendukuri,[1] Lucie Blais,[2] & Jacques LeLorier[3]

[1]*Department of Clinical Epidemiology and Community Studies, St Mary's Hospital, Montreal and Department of Epidemiology and Biostatistics, McGill University, Montreal,* [2]*Faculté de Pharmacie, Université de Montréal and* [3]*Centre de recherche, Centre hospitalier de l'Université de Montréal CHUM-Hôtel-Dieu, Montréal, Québec, Canada*

Aims There is evidence that large doses of inhaled corticosteroids lead to an increased risk of glaucoma, cataracts and other problems associated with oral corticosteroid use. However, no formal investigation so far has been conducted into the relationship between inhaled corticosteroids and diabetes.

Methods Our nested case-control design studied the association between current use of inhaled corticosteroids and the risk of using antidiabetic medications among a cohort of 21 645 elderly subjects. We also investigated the possibility of a dose–response relationship in users of beclomethasone. Data were obtained from the medical and pharmaceutical databases of the Regie de l'assurance maladie du Québec.

Results Within the cohort, we identified 1494 cases and we selected 14 931 controls using density sampling. The unadjusted rate ratio (and 95% confidence interval, CI) for developing diabetes among current users of inhaled corticosteroids was 1.4 (1.2, 1.5). After adjusting for covariates, the rate ratio (95% CI) decreased to 0.9 (0.8, 1.1). The loss of statistical significance was due in large part to adjusting for the current use of oral corticosteroids. We also did not observe a statistically significant increase in risk among users of high-dose beclomethasone compared to nonusers, after adjusting for covariates.

Conclusions Our results do not indicate an increased risk of diabetes among current users of inhaled corticosteroids.

Keywords: beclomethasone, diabetes, elderly, inhaled corticosteroids, nested case-control design, pharmaceutical database

Introduction

Over the last decade, inhaled corticosteroids have emerged as the first-line therapy for asthma because of their proven efficacy in controlling chronic inflammation, which is central to the pathogenesis of this disease. These drugs have been shown to be clinically effective in reducing airway hyper-responsiveness, decreasing the frequency of acute exacerbations, and diminishing symptoms [1]. They are also widely prescribed for patients with chronic obstructive pulmonary disease, though their efficacy among these patients is yet to be proven. Published guidelines for the management of asthma recommend the use of inhaled corticosteroids, both in the early course of the disease, as preventive therapy, and in its chronic treatment [2]. Consequently, there has been a steady increase in the prescription of inhaled corticosteroids.

Inhaled corticosteroids are preferred to oral corticosteroids because, even at high doses, they present a reduced risk of adverse systemic effects. Studies on the pharmacokinetics of inhaled corticosteroids show that they also have low oral bioavailability, i.e. they are less likely to be swallowed than inhaled, and high pulmonary bioavailability, i.e. a large percentage of the drug is absorbed systemically from the lungs [3]. Though there is no conclusive evidence [4], several investigations have documented that augmented systemic absorption of large doses of inhaled corticosteroids leads to increased adrenal suppression [5, 6], glaucoma [7], cataract formation [8, 9], osteoporosis [10, 11], and decreased growth in children [12, 13].

It is well-established that oral corticosteroids can cause diabetes mellitus even when taken over a short period of time [14]. There is evidence that the risk and magnitude of this side-effect is greater in elderly patients [15]. Faul

Correspondence: Jacques LeLorier, MD, PhD, Centre de recherche, CHUM-Hôtel-Dieu, 3850 Saint-Urbain, Montréal, Québec, Canada H2W 1T8. Tel.: (514) 890-8110; Fax: (514) 843 2774; E-mail: jaques.le.lorier@umontreal.ca

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and colleagues reported a case study in which high doses of an inhaled corticosteroid, fluticasone propionate, were found to result in a loss of diabetic control [16]. To the best of our knowledge, no randomized or non-experimental (observational) investigation in the published literature has examined the effect of inhaled corticosteroids on the risk of diabetes mellitus. In this paper, we scrutinized the possible risk of diabetes among elderly subjects currently using inhaled corticosteroids, via a nested case-control design. In particular, we investigated whether users of high doses of beclomethasone are at increased risk of taking antidiabetic medication compared with nonusers of inhaled corticosteroids.

Methods

Data source

Information on patients' drug intake and utilization of medical services was obtained from the computerized databases of the Régie de l'assurance-maladie du Québec (RAMQ), which is the government-administered health insurance organization for the Canadian province of Quebec. At the time of this study, between January 1, 1989 and June 30, 1996, the cost of prescription medication and medical services for all residents over the age of 65 years was chiefly covered by the RAMQ. Between January 1, 1993 and June 30, 1996, patients paid a $2.00 fee for each prescription filled. About 97% of the eligible population was registered under this plan in 1990. The databases maintained by the RAMQ for administrative purposes have found extensive use in pharmaco-epidemiological research [12, 13, 17, 18], and a recent study [19] established that they were comprehensive and valid for this purpose. The drug database includes information on the name of the drug, date of filling the prescription, dosage, format, quantity dispensed, and duration for which the drug was prescribed. It does not include drugs that may be dispensed during a stay in hospital or some nursing homes. The medical services database, which records details of diagnostic and therapeutic procedures received during physician visits or hospitalizations, was accessed to obtain information on demographic variables, such as age, sex, date of death as well as frequency of utilization of health services. The different databases were linked by the unique identification number assigned to each subject, which is encrypted to maintain confidentiality.

Study cohort

We examined a cohort of 21 645 subjects who had been identified earlier for a study on the use of antibiotics in the treatment of acute exacerbations of chronic pulmonary disease. This cohort consisted of subjects who had either (i) filled two or more prescriptions for an inhaled bronchodilator on at least one occasion during the course of any single year between January 1, 1989 and June 30, 1996, or (ii) received at least 6 months of treatment with an oral bronchodilator, during the same period of time. For the current study, the date of entry of a subject into the cohort was defined as the date of first prescription for a bronchodilator on or after January 1, 1989. Only subjects who were 66 years or older on their date of entry were retained. This ensured that information on drug use was available for up to 1 year prior to the entry date for each subject. We also eliminated subjects who had a prescription for a diabetic drug in the year prior to their entry into the cohort to ensure that we were looking at incident cases of diabetes only. Cohort members were then followed until their death or June 30, 1996, whichever occurred first.

Identification of cases and controls

Cases were defined as subjects who had received a prescription for an antidiabetic medication following entry into the cohort. Medication for diabetes included insulin or oral antidiabetic agents (acetohexamide, chlorpropamide, glyburide, metformin, tolbutamide and acarbose). The index date for a case was the date corresponding to the receipt of this prescription. Matching controls were selected for each case from among all subjects present in the cohort on the index date, employing a density sampling approach [20]. This means a subject could serve as a control prior to becoming a case. Also, a subject could serve as a control to more than 1 case at the same time or at different times. Up to 10 controls were selected for each case. Cases and controls were matched for their year and month of entry into the cohort. Density sampling enabled us to estimate a rate ratio for comparison of users and nonusers of inhaled corticosteroids.

Inhaled corticosteroid exposure

Current exposure to an inhaled corticosteroid was defined as filling a prescription for beclomethasone, budesonide, flunisolide, fluticasone or triamcinolone in powder, aerosol or solution format, such that the period for which the drug was dispensed overlapped with the period 2 weeks prior to and including the index date. Low- and high-doses of beclomethasone were defined as 50 μg/puff and 250 μg/puff, respectively.

Covariates

Since users of inhaled corticosteroids are likely to take oral corticosteroids and since the relationship between

oral corticosteroids and diabetes is well established, oral corticosteroid usage is an important confounding variable of the relationship under study. Current exposure to an oral corticosteroid was defined in the same way as for inhaled corticosteroids. We used three different measures of comorbidity: (1) number of physician visits, (2) number of hospitalizations, in the year prior to the index date, and (3) number of concurrent prescriptions filled on the index date (excluding those for inhaled and oral corticosteroids, bronchodilators and antidiabetic agents). A trichotomous variable was adopted to measure the number of hospitalizations: no hospitalization, 1–3 hospitalizations, and more than 3 hospitalizations in the year prior to the index visit. Physician visits were also measured by a trichotomous variable with levels: 0–24 visits per year, 25–48 visits per year, and more than 48 visits per year. The number of concurrent prescriptions was treated as a dichotomous variable: no concurrent prescriptions and one or more concurrent prescriptions. Age at the index date and gender were also adjusted. Subjects were divided into three age categories: 65–74.9 years, 75–84.9 years, and 85 years and over.

Statistical analysis

Descriptive statistics served to compare the cases and controls with respect to demographic characteristics, oral corticosteroid use, and comorbidity. The adjusted rate ratio for developing diabetes among current users of inhaled corticosteroids compared with nonusers was estimated using a proportional hazards model. As discussed in Prentice & Breslow (1978) [21] this approach is suitable for a matched-case control study. Two types of models were fitted. In the first, the independent variable measuring exposure was dichotomous and compared all current users of inhaled corticosteroids with all nonusers. In the second model, we investigated a dose–response relationship among users of beclomethasone. The independent variable measuring exposure in the second model separately compared low- and high-dose users of beclomethasone with nonusers of inhaled corticosteroids. As an alternative approach to adjusting for oral corticosteroid use, we also fitted the first model, after eliminating all current users of oral corticosteroids. Rate ratios were considered statistically significant when their 95% confidence interval did not include 1. All statistical analyses were performed with the SAS software package [22].

Results

There were 1494 eligible cases among 21 645 subjects after eliminating those who were less than 66 years of age at entry and subjects who had taken antidiabetic medications in the year prior to cohort entry. Density sampling yielded 14 931 controls. The characteristics of cases and controls are summarized in Table 1. Age distribution was similar among cases and controls. There was a larger percentage of women among the cases (37.2%) than among the controls (30.8%). Of the cases, 34.5% were current users of inhaled corticosteroids compared with 28.1% of the controls. Similarly, there was a greater percentage of subjects among the cases who were exposed to oral corticosteroids (24.2%) compared with the controls (7.6%). Co-morbidity was found to be much higher among the cases than among the controls: 64.7% of cases had more than 48 physician visits in the year prior to the index date (i.e. more than two visits per month), compared with 53.9% of the controls. Similarly, 61.3% of cases had more than three hospitalizations in the year prior to the index date, compared with 46.8% of the controls. Finally, 47% of cases had one or more concurrent prescriptions (for drugs other than an inhaled or oral corticosteroid, bronchodilator or antidiabetic agent), dispensed for a period including the index date, compared with 13.5% of controls. A larger percentage of cases than controls had filled a prescription for high-dose beclomethasone.

Table 1 Demographic and clinical characteristics of the case-control study population.

	Cases (%) (Total = 1494)	*Controls (%) (Total = 14 931)*
Age (years)		
65–74.9	60.0	55.9
75–84.9	34.3	36.8
≥85	5.7	7.3
Gender		
Male	62.8	69.2
Female	37.2	30.8
Current users of inhaled corticosteroids	34.5	28.1
Current users of oral corticosteroids	24.2	7.6
Current users of beclomethasone		
Dose I	8.5	8.7
Dose II	17.1	12.0
Number of concurrent prescriptions		
0	53.0	86.5
≥1	47.0	13.5
Number of physician visits		
0–24	13.3	20.9
25–48	22.0	25.2
>49	64.7	53.9
Number of hospitalizations		
0	7.0	12.6
1–3	31.7	40.6
>3	61.3	46.8

Table 2 Results of conditional logistic regression analysis of the relationship between current use of inhaled corticosteroids and use of antidiabetics ($n = 16\,425$).

	Rate ratio	*95% confidence interval*
Crude model		
IC* use		
Non-user	1.0	–
Any IC use	1.4	1.2, 1.5
Adjusted model		
IC use		
Non-user	1.0	–
Any IC use	0.9	0.8, 1.1
Oral corticosteroids		
No	1.0	
Yes	2.9	2.5, 3.3
Age (years)		
65–74.9	1.0	–
75–84.9	0.8	0.7, 0.9
>85	0.7	0.5, 0.9
Gender		
Male	1.0	
Female	1.3	1.2, 1.5
Number of concurrent prescriptions		
0	1.0	
>1	2.2	1.9, 2.5
Physician visits		
0–24	1.0	
25–48	1.2	1.0, 1.5
>48	1.5	1.2, 1.8
Hospitalizations		
0	1.0	
1–3	1.3	1.0, 1.6
>3	1.6	1.3, 2.1

*Inhaled corticosteroid.

Table 3 Results of conditional logistic regression analysis of the dose–response relationship between current use of Beclomethasone and use of antidiabetics ($n = 15\,187$).

	Rate ratio	*95% confidence interval*
Crude model		
IC* use		
Non-user	1.0	
Beclomethasone-Dose I	1.1	0.9, 1.3
Beclomethasone-Dose II	1.6	1.4, 1.9
Adjusted model		
IC use		
Non-user	1.0	–
Beclomethasone-Dose I	0.8	0.7, 1.0
Beclomethasone-Dose II	1.4	0.9, 1.2
Oral corticosteroids		
No	1.0	–
Yes	2.7	2.3, 3.2
Age (years)		
65–74.9	1.0	–
75–84.9	0.8	0.7, 0.9
>85	0.7	0.5, 0.9
Gender		
Male	1.0	–
Female	1.3	1.1,1.5
Number of concurrent prescriptions		
0	1.0	–
>1	2.2	1.9, 2.5
Physician visits		
0–24	1.0	–
25–48	1.2	1.0, 1.5
>48	1.4	1.2, 1.8
Hospitalizations		
0	1.0	–
1–3	1.2	1.0, 1.6
>3	1.6	1.2, 2.0

*Inhaled corticosteroid. Beclomethasone dose I refers to low dose (50 μg/puff, while dose II refers to high dose (250 μg/puff).

Table 2 lists the unadjusted and adjusted rate ratios and 95% confidence intervals (CI) for usage of antidiabetic agents, comparing currently exposed to -unexposed subjects. The crude rate ratio (95% CI) for filling a prescription for an antidiabetic medication among all current users of inhaled corticosteroids compared to nonusers was 1.4 (1.2, 1.5). The corresponding adjusted rate ratio (95% CI) was 0.9 (0.8, 1.1), indicating the absence of a statistically significant effect. The adjusted rate ratio (95% CI) associated with oral corticosteroid use was 2.9 (2.5, 3.3), suggesting a strong effect of oral corticosteroid use. Female gender, more than one concurrent prescription, more than 48 physician visits and more than three hospitalizations in the year prior to the index date were statistically significant predictors of antidiabetic use. When the same model was fitted after eliminating current users of oral corticosteroids, the rate ratio associated with current use of inhaled corticosteroids remained nonsignificant (rate ratio: 0.9, 95% CI: 0.8, 1.0).

Table 3 lists the results of dose–response analysis for users of beclomethasone compared to all nonusers of inhaled corticosteroids. The crude rate ratio (95% CI) for low-dose beclomethasone was 1.1 (0.9, 1.3), and for high-dose beclomethasone it was 1.6 (1.4, 1.9). After adjustment for covariates, the rate ratio (95% CI) among users of low-dose and high-dose beclomethasone was 0.8 (0.7, 1.0) and 1.0 (0.9, 1.2), respectively. Once again, current oral corticosteroid usage was a strong predictor of antidiabetic usage, along with female gender, more than one concurrent prescription, and increased number of physician visits and hospitalizations.

Discussion

The potentially adverse systemic effects that inhaled corticosteroids could cause, when administered in high

doses, have been a matter of concern ever since their introduction [23]. In our study, we have tried to estimate the effect of current inhaled corticosteroids on the risk of developing diabetes mellitus, employing data on drug-dispensation from administrative databases. The results suggest that current exposure, as we have measured it, does not lead to a significantly increased risk of diabetes, after adjusting for other variables, particularly the simultaneous use of oral corticosteroids.

Since antidiabetic drugs are taken exclusively to treat diabetes, the possibility of misclassifying nondiseased subjects as diseased subjects is minimal. However, an important concern is that Type II diabetes is asymptomatic in its early stages, and a notoriously under-treated and under-diagnosed disease. Our finding that the risk of receiving an antidiabetic prescription decreases with age despite the knowledge that glucose tolerance increases with age, highlights this concern. During the time period covered by this study, there was no particular awareness of an association between inhaled corticosteroid use and diabetes mellitus. Therefore, it is likely that most cases were a fortuitous finding, resulting in significant under-ascertainment of cases. However, since this underestimation is nondifferential with respect to exposure it would not have biased the estimation of the rate ratio [24]. We matched patients for the month and year of their entry into the cohort to adjust for variations in drug prescription patterns across the study period. This also controlled for seasonal variation in the onset and severity of chronic airway disease and the consequent use of antiasthma medication. A limitation of our study is that we were not able to measure and control for risk factors for diabetes, such as family history and obesity.

Systemic glucocorticoid therapy causes hyperglycaemia and therefore worsens diabetes mellitus. These risks are particularly serious for elderly subjects since glucose tolerance decreases with age. Even low doses of oral cortiosteroid therapy can produce glucose intolerance, requiring that older patients with a history of the disease be monitored carefully [25]. Our study does not demonstrate a statistically significant increase in the risk of diabetes among current users of inhaled corticosteroids. However, this question needs to be investigated further after addressing the drawbacks we have identified here, particularly the method of ascertainment of Type II diabetes.

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References

1 Barnes PJ. Efficacy of inhaled corticosteroids in asthma. *J Allergy Clin Immunol* 1998; **102**: 531–538.
2 Georgitis JW. The 1997 Asthma Management Guidelines and therapeutic issues relating to the treatment of ashmaashma. National Heart Lung and Blood Institute. *Chest* 1999; **115**: 210–217.
3 Derendorf H, Hochhaus G, Meibohm B, Mollmann H, Barth J. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol* 1998; **101**: S440–S446.
4 Barnes PJ. Current issues for establishing inhaled corticosteroids as the antiinflammatory agents of choice in asthma. *J Allergy Clin Immunol* 1998; **101**: S427–S433.
5 Brown PH, Blundell G, Greening AP, Crompton GK. Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. *Resp Med* 1991; **85**: 501–510.
6 Goldberg S, Algur N, Levi M, *et al*. Adrenal suppression among asthmatic children receiving chronic therapy with inhaled corticosteroid with and without spacer device. *Ann Allergy, Asthma Immunol* 1996; **76**: 234–238.
7 Garbe E, LeLorier J, Boivin J-F, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA* 1997; **277**:
8 Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997; **337**: 8–14.
9 Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroids with cataract extraction in elderly patients. *JAMA* 1998; **280**: 539–543.
10 Meeran K, Hattersley A, Burrin J, Shiner R, Ibertson K. Oral and inhaled corticosteroids reduce bone formation as shown by plasma osteocalcin levels. *Am J Resp Crit Care Med* 1995; **151**: 333–336.
11 Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994; **105**: 1722–1727.
12 Allen DB, Mullen M, Mullen B. A meta-analysis of the effects of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994; **93**: 967–976.
13 Wolthers O, Pedersen S. Short term growth during treatment with inhaled fluticasone dipropionate and beclomethasone dipropionate. *Arch Dis Children* 1993; **68**: 673–676.
14 Skorodin MS. Pharmacotherapy for Asthma and Chronic Obstructive Pulmonary Disease: current thinking, practices and controversies. *Arch Intern Med* 1993; **153**: 814–828.
15 Thomas TP. The complications of systemic corticosteroid therapy in the elderly: a retrospective study. *Gerontology* 1984; **30**: 60–65.
16 Faul JL, Tormey W, Tormey V, Burke C. High dose inhaled corticosteroids and dose dependent loss of diabetic control. *Br Med J* 1998; **317**: 1491.
17 Garbe E, LeLorier J, Boivin J-F, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. *Lancet* 1997; **350**: 979–982.
18 Garbe E, Suissa S, LeLorier J. Exposure to allupurinol and the risk of cataract extraction in elderly patients. *Arch Ophthalmol* 1998; **116**: 1652–1656.

19 Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. *J Clin Epidemiol* 1995; **48**: 999–1009.

20 Lubin JH, Gail MH. Biased selection of controls for case-control analyses of cohort studies. *Biometrics* 1984; **40**: 63–75.

21 Prentice RL, Breslow NE. Retrospective studies and failure time models. *Biometrika* 1978; **65**: 153–158.

22 SAS Institute Inc. SAS/STAT Software. Changes and enhancements through release 6. *12 Cary, NC SAS Inst Inc*, 1997; **219–46**: 871–948.

23 Barnes PJ. Glucocorticosteroids. In *Asthma: Basic Mechanisms and Clinical Management*, 3rd edn. London: Academic Press 1998: 725–766.

24 Rothman KJ, Greenland S. *Modern Epidemiology*, 2nd edn. Philadelphia: Lippincott-Raven, 1998.

25 Bloom JW. Pharmacological management of asthma in the elderly, 1997.

