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Inhaled corticosteroids and hospitalisation due to exacerbation of COPD

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Inhaled corticosteroids and hospitalisation due to exacerbation of COPD. J. Bourbeau, P. Ernst, D. Cockcoft, S. Suissa. ©ERS Journals Ltd 2003.

ABSTRACT: Previous studies have provided conflicting evidence as to the possible benefits of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease (COPD).

Using the Saskatchewan healthcare databases subjects were identified who were aged ⩾55 yrs, initiating regular treatment for COPD but without any prior treatment for asthma. In the current nested case-control analysis, the authors concentrated on 1,742 subjects with a first hospitalisation for COPD after January 1, 1990 and examined whether the use of inhaled corticosteroids was associated with a change in the risk of a subsequent hospitalisation for COPD.

The cases consisted of 846 patients with a subsequent hospitalisation for COPD. These were matched on age, time since the prior hospitalisation and use of other respiratory therapy to all possible person moments in the cohort without rehospitalisation. After further adjustment for comorbidity, sex, calendar year and intensity of other drug therapy, inhaled corticosteroids were not significantly associated with risk of a subsequent COPD hospitalisation. Even relatively high doses of inhaled corticosteroids, >800 μg of beclomethasone or the equivalent per day, were not associated with the risk of COPD hospitalisation.

No reduction in chronic obstructive pulmonary disease exacerbations requiring hospitalisation, in relation to the use of inhaled corticosteroids, were observed.

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Despite the limited evidence for the efficacy of inhaled corticosteroids in chronic obstructive pulmonary disease (COPD), as opposed to asthma, these medications are widely prescribed in patients with both disorders [1, 2]. The limited number of studies that have evaluated the effect of inhaled corticosteroids on airway inflammation in COPD have not demonstrated a suppressive effect, even at high doses [3, 4]. Several major long-term, randomised, clinical trials have been unable to show a benefit of the regular use of inhaled corticosteroids on the accelerated decline in lung function characteristic of COPD [5–8]. In contrast, a recent meta-analysis of nine randomised trials, which followed a total of 3,976 patients for a minimum of 6 months, reported an estimated 30% reduction in exacerbations with the use of relatively large doses of inhaled corticosteroids [9]. In line with these findings, a recent Canadian cohort study suggested a strong protective effect of inhaled corticosteroids on the risk of rehospitalisation for an exacerbation of COPD among patients previously hospitalised with this indication [10].

The authors attempted to confirm whether treatment with inhaled corticosteroids resulted in a reduction in the risk of severe exacerbations requiring hospitalisation in a different population of patients with COPD. Particular attention was given to excluding patients with asthma and to examining details of exposure, such as dose and timing in relation to rehospitalisation.

Methods

Source of data

The computerised administrative databases of the Saskatchewan universal healthcare insurance system were the primary source of information for the present study. These databases have been used extensively in the past and have been shown to be both comprehensive and valid [11].

Over 99% of Saskatchewan residents (~1 million) receive publicly funded healthcare and of these ~91% are eligible for outpatient prescription drug benefits. Dispensed prescriptions listed on the provincial formulary, use of healthcare services (*e.g.* hospital stays and physician services) and vital status information are all recorded and the information can be linked for each individual using a unique health services′ number.

Study subjects

A source population was first identified, aged ⩾55 yrs, who had been dispensed at least one prescription of any inhaled or oral β-agonist, xanthine or ipratropium bromide between September 1, 1980–December 31, 1997. Only subjects with more than occasional treatment, those with new-onset airway disease and subjects without prior asthma were included.

Therefore, those subjects who had been dispensed a minimum of at least three prescriptions on two different dates in any 1-yr period and who had not received any β-agonist, xanthine preparation, antiasthma drug (cromolyn, nedocromil or ketotifen), nasal or inhaled corticosteroid in the prior 5 yrs were selected. The cohort identified for the purposes of the present report, consisted of the 1,742 subjects with a first hospitalisation with a primary diagnosis of COPD after January 1, 1990, the approximate time when high-dose inhaled corticosteroid therapy became generally available [2]. Cohort entry was taken as the date of discharge from this first hospitalisation for COPD. All patients in the cohort were followed up to December 31, 1999 at the earliest, occurrence of a subsequent COPD hospitalisation, emigration from the province or death.

To permit a precise assessment of exposure to inhaled corticosteroids in relation to the timing of a rehospitalisation and to allow tight matching of subjects to compare patients of similar severity, a nested-case control strategy was used within this cohort of patients. Case patients were defined as those who were rehospitalised with a primary discharge diagnosis of COPD. The date of the first rehospitalisation for COPD was taken as the "index date". For each case, the control person moments were taken from all subjects who were still in the cohort and had not been rehospitalised for COPD by the index date of the case patient. Practically, this means that a cohort member may serve as a control before becoming a case. This is required for the unbiased analysis of nested case-control studies [12, 13]. Furthermore, cohort members may have been chosen as controls at several different points in time, in order to provide control person moments for comparison. These control person moments were also matched on age, time since the first hospitalisation for COPD, dispensing or not of >18 canisters of β-agonists in the 12 months prior to the date of rehospitalisation of the case, use of a home oxygen service at any time and dispensing within 30 days of the rehospitalisation date of a prescription for each of xanthines, nebulised bronchodilators, oral corticosteroids and antibiotics.

Categorisation of inhaled corticosteroid use

Use of inhaled corticosteroids was considered in relation to the timing of rehospitalisation for COPD or the matching index date for the controls, according to several different definitions. "Any use" was defined as the dispensing of one or more prescriptions for an inhaled corticosteroid in the year prior to the index date. "Current use" was defined by a prescription being dispensed within 60 days of the index date for the high-dose formulations (mostly beclomethasone 250 μg·inhalation^{-1}) and 30 days for the low-dose formulations (mostly beclomethasone 50 μg·inhalation^{-1}). "Past use" defined the exposure for subjects with any use but not current use. Finally, cumulative exposure in the prior year was calculated according to the following equivalencies: beclomethasone 1,000 μg equal to budesonide 800 μg equal to fluticasone 500 μg equal to flunisolide 2,000 μg equal to triamcinolone 2,000 μg. Cumulative exposure in the year prior to the index date was converted to a mean daily dose by dividing the cumulative dose by the number of days in the prior year during which the subject was not hospitalised. Mean daily dose was categorised as: ⩽400 μg, 401–800 μg and >800 μg.

Statistical analysis

Conditional logistic regression was used with the matched case-control sets to estimate the odds ratios as an approximation of the rate ratios for the association of inhaled corticosteroids and a subsequent COPD hospitalisation. Adjustment of these rate ratios was carried out to account for differences in risk factors that may remain after matching. Adjustments were made for age (measured as a continuous factor) at index date, sex, number of hospitalisations for health problems other than COPD in the year prior to the index time, calendar year (to adjust for secular trends), number of canisters of inhaled β-agonists, number of prescriptions for oral corticosteroids, nebulised bronchodilatators, xanthines, ipratropium inhalers and antibiotics in the year prior to index date.

Results

The cohort included 1,742 subjects who had been hospitalised for COPD. Of these, 846 were readmitted to hospital for COPD during the follow-up. For 573 of these case patients, matching was within 1 yr of age, for 102 within 2 yrs, for 58 within 3 yrs and for 95 cases the matching on age was less precise. For three cases, no match could be found. The remaining 843 cases were matched to 11,030 control person moments. Table 1 provides a comparison between various characteristics of the cases and the control person moments. There were more males among the cases. As expected from the matching, age, duration of follow-up after the first hospitalisation for COPD and the number of canisters of β-agonists dispensed was similar in cases and controls. Cases had more hospitalisations for problems other than COPD and used, on average, more respiratory medications including oral corticosteroids and antibiotics. Prescriptions for the latter two groups of medications occurred approximately once each in the prior year, suggesting these medications were prescribed intermittently for exacerbations of COPD that did not necessarily lead to rehospitalisation.

In table 2 rate ratios for the relationship between any, current or past use of inhaled corticosteroids in the prior year and risk of a COPD hospitalisation are close to unity and

Table 1. – Characteristics of study patients selected as cases and controls

	Cases	Control person-moments
Subjects n	843	11030
Males %	66	62
Age yrs	76.2±7.6	76.1±6.6
Follow-up yrs	1.28±1.51	1.28±1.09
Hospitalisations not for COPD in prior year	0.76±1.4	0.60±1.1
Drug dispensed in prior year		
Inhaled β_2-agonist	459 (54) 4.69±9.6#	4376 (46) 4.64±11.5#
Ipratropium bromide	284 (34) 1.90±3.9#	2563 (26) 1.32±2.5#
Nebulised therapy	278 (33) 3.03±6.3#	2562 (28) 2.44±4.6#
Xanthines	214 (25) 1.51±3.4#	2169 (25) 1.37±2.4#
Oral corticosteroids	258 (31) 1.12±2.5#	2144 (24) 0.82±1.7#
Inhaled corticosteroids	416 (49) 2.49±3.8#	4351 (49) 2.11±2.8#
Antibiotics	432 (51) 1.14±2.2#	4306 (43) 1.07±1.6#

Data are presented as n (%) or mean±SD unless otherwise stated. COPD: chronic obstructive pulmonary disease. #: number of canisters of β-agonists and number of prescriptions dispensed for the remainder of the medications.

Table 2. – Matched rate ratios for chronic obstructive pulmonary disease (COPD) hospitalisation according to any, current and past use of inhaled corticosteroids

Use of inhaled corticosteroids in past year	Cases n	Controls[#] n	Crude rate ratio	Adjusted[¶] rate ratio (95% CI)
Total	843	11030		
No use	427	6679	Reference	
Any use	416	4351	1.20	1.07 (0.91–1.27)
Current use	275	2994	1.16	1.02 (0.85–1.22)
Past use	141	1357	1.30	1.19 (0.95–1.49)

Matched for age, time since first hospitalisation, current use of antibiotics, nebulised bronchodilatators, oral corticosteroids and xanthines, dispensing of $\geqslant$18 canisters of inhaled β-agonists in the year prior to the index date and prescription of home oxygen at anytime prior to index date. CI: confidence interval. [#]: all possible control person moments among the 1742 subjects with an initial hospitalisation for COPD after January 1, 1990 before a subsequent hospitalisation occurred and who were still in the cohort at the time of the index date of the case to which they are matched; [¶]: adjusted as stated in text.

Table 3. – Matched rate ratios for chronic obstructive pulmonary disease (COPD) hospitalisation according to the mean daily dose of inhaled corticosteroids

Use of inhaled corticosteroids in past year	Cases n	Controls[#] n	Crude rate ratio	Adjusted[¶] rate ratio (95% CI)
Total	843	11030		
None	427	6679	Reference	
$\leqslant$400 μg	100	1233	1.20	1.11 (0.87–1.41)
401–800 μg	85	1019	1.05	0.97 (0.74–1.26)
>800 μg	90	742	1.22	0.95 (0.72–1.27)

Matched for age, time since first hospitalisation, current use of antibiotics, nebulised bronchodilatators, oral corticosteroids and xanthines, dispensing of $\geqslant$18 canisters of inhaled β-agonists in the year prior to the index date and prescription of home oxygen at anytime prior to index date. CI: confidence interval. [#]: all possible control person moments among the 1742 subjects with an initial hospitalisation for COPD after January 1, 1990 before a subsequent hospitalisation occurred and who were still in the cohort at the time of the index date of the case to which they are matched; [¶]: adjusted as stated in text.

the confidence intervals include one suggesting no significant association. A more precise measure of inhaled corticosteroid use during the year prior to rehospitalisation also fails to demonstrate any association even at mean daily doses >800 μg of beclomethasone or the equivalent (table 3).

Discussion

The authors examined whether the use of inhaled corticosteroids may influence the risk of a new severe exacerbation of COPD among patients who experienced a prior COPD exacerbation requiring hospitalisation. No apparent influence of inhaled corticosteroids could be found, even at moderate-to-high doses, on the likelihood of a subsequent hospitalisation for COPD exacerbation.

The strengths of the present study are the inclusion of all patients in the general population receiving medications commonly prescribed for the treatment of COPD and hospitalised for this condition. The assessment of the use of inhaled corticosteroids is considered complete because the provincial drug plan is the primary insurer of Saskatchewan formulary benefits (therefore claims must be processed through the drug plan's online system) and the drugs of interest are listed on the Formulary.

Complete information on dispensed medications allowed the examination of the possibility of a dose/response relationship between the use of inhaled corticosteroids and the risk of being rehospitalised for COPD. There was no evidence of increasing benefit with increasing doses of these medications. Information on dispensing of other respiratory medications, such as bronchodilators, antibiotics and oral corticosteroids was also used to adjust for differences in severity of COPD between those rehospitalised and those who were not. Since the nature of a rehospitalisation may differ according to when in time it occurs, cases and control person moments were matched on the length of time from the first hospitalisation, so as not to compare rehospitalisations occurring early *versus* later. To avoid differences in secular trends in prescribing or in hospitalisations, the matched rate ratios were further adjusted for the year in which the hospitalisation occurred. The influence of comorbid conditions were accounted for by adjusting for differences in hospitalisations for problems other than COPD.

A potential weakness of this study is in the validity of the diagnosis of COPD. It was assumed that subjects requiring a minimum of three bronchodilator prescriptions over a 1-yr period, for the first time starting after the age of 55 yrs, were likely to have COPD. This is especially likely since all subjects with prior use of drugs such as inhaled and nasal corticosteroids, treatments more commonly used for asthma before the age of 55 yrs, were eliminated from consideration. In support of the likelihood that subjects included in the current analysis did in fact suffer from COPD is the fact that all subjects entered the cohort with a hospitalisation where the primary discharge diagnosis was COPD. A previous validation study of the Saskatchewan databases has shown the hospitalisation diagnosis of COPD to be quite accurate, as long as no attempt is made to differentiate asthma from COPD and that both disorders are considered together [14]. As with most database studies, access was unavailable to primary medical records, which might provide smoking and lung function information that could be used to reinforce the diagnosis of COPD and better assess severity in the cohort of patients.

These results contrast most directly with the recent study by Sin and Tu [10] who also used Canadian healthcare databases, albeit from another province. Among subjects $\geqslant$65 yrs

of age, discharged from hospital in the province of Ontario with a diagnosis of COPD, one or more prescriptions of an inhaled corticosteroid dispensed within 90 days of hospital discharge was associated with a 24% reduction in the risk of a subsequent COPD hospitalisation occurring within the following year. There were several differences in the methods used by SIN and TU [10] and the current study. A specific effort to exclude patients with asthma as opposed to COPD was made in the present study. The use of a nested case-control analysis allowed the examination, in detail, of the use of inhaled corticosteroids in the time period preceding rehospitalisation for COPD. By comparison, SIN and TU [10] categorised exposure based on the dispensing of inhaled corticosteroids within a short period after the previous hospitalisation and linked this to a subsequent hospitalisation occurring up to 1 yr later. In the present study, an incident as opposed to a prevalent cohort of patients was selected to assure that subjects examined were at similar points in the natural history of their disease. Any, or all, of these differences in methodology may have led to the differences in results found in these two database studies.

A recent meta-analysis including nine randomised clinical trials with a treatment period of $\geqslant$6 months, concluded that high doses of inhaled corticosteroids (in all but one study inhaled corticosteroids were given at a dose equivalent to beclomethasone $\geqslant$1,000 $\mu g \cdot day^{-1}$) reduced exacerbations by 30% [9]. Exacerbations were defined in various ways, but in the majority, did not require hospitalisation. The present study cannot exclude the possibility that high doses of inhaled corticosteroids prevent such milder exacerbations. The doses used by the study subjects were somewhat lower than those used in these clinical trials, so that possible reductions in severe exacerbations that may result from the use of higher doses of inhaled corticosteroids cannot be ruled out. However, it should be noted that no dose/response in the data was observed nor was any benefit demonstrated among subjects who had been dispensed a mean daily dose of >800 μg of the inhaled corticosteroid beclomethasone or equivalent.

To conclude, using a design and sources of information, which have previously allowed the demonstration of reduced hospitalisations with the use of inhaled corticosteroids in patients with asthma [15, 16], the authors were unable to show any benefit of inhaled corticosteroids on reducing severe exacerbations requiring hospitalisation among patients with chronic obstructive pulmonary disease. These results are therefore not consistent with a previous report of a significant benefit of inhaled corticosteroids in reducing rehospitalisation for chronic obstructive pulmonary disease. This inconsistency suggests that the results of ongoing clinical trials, specifically designed to look at the possible benefits of inhaled corticosteroids on the risk of exacerbation, should be awaited before recommending the use of inhaled corticosteroids for this indication.

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