Inhaled Corticosteroids and the Risk of Mortality and Readmission In Elderly Patients with Chronic Obstructive Pulmonary Disease

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There is considerable controversy concerning the utility of inhaled corticosteroids for the long-term treatment of patients with COPD. Recent studies have suggested that although inhaled corticosteroids do not alter the rate of decline in lung function, they may reduce airway hyperresponsiveness, decrease the frequency of exacerbations, and slow the rate of decline in the patients' health status. The relationship between inhaled corticosteroids and subsequent risk of hospitalization or mortality remains unknown. We therefore conducted a population-based cohort study using administrative databases in Ontario, Canada (n = 22,620) to determine the association between inhaled corticosteroid therapy and the combined risk of repeat hospitalization and all-cause mortality in elderly patients with COPD. Patients who received inhaled corticosteroid therapy postdischarge (within 90 d) had 24% fewer repeat hospitalizations for COPD (95% confidence interval [CI], 22 to 35%) and were 29% less likely to experience mortality (95% CI, 22 to 35%) during 1 yr of follow-up after adjustment for various confounding factors. This cohort study has suggested that inhaled corticosteroid therapy is associated with reduced COPD-related morbidity and mortality in elderly patients. Although not definitive, because of the observational nature of these findings, these data provide a compelling rationale for a large randomized trial to determine the effect of inhaled corticosteroids on COPD-related morbidity and mortality.

Keywords: chronic obstructive pulmonary disease; inhaled corticosteroids; hospitalization; mortality

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of mortality in North America (1). Because COPD is the only major disease whose mortality is increasing, by the year 2020, it will be the third most important cause of death worldwide (2). With the projected increase in the prevalence and severity of COPD over the next two decades, novel management strategies are required to effectively deal with the growing COPD burden in the community.

There is considerable evidence that airway inflammation plays an important role in the pathogenesis of COPD (3), and use of anti-inflammatories such as orally administered corticosteroids has been associated with an accelerated rate of resolution of patient symptoms and improved prognosis, particularly during exacerbations (4, 5). However, their long-term use is generally precluded on the basis of significant systemic toxicity (6). In contrast, inhaled corticosteroids appear to have a more favorable toxicity profile, making it an attractive alternative to oral preparations (7). However, there remains considerable controversy concerning their utility for the chronic management of COPD (8, 9).

Previous studies have shown that inhaled corticosteroids do not decelerate the rate of decline in expiratory flow volumes over time in patients with mild to moderate COPD (10, 11). However, a recent study has suggested that inhaled corticosteroids may slow the rate of decline in (disease-specific) health status of patients and reduce the risk of clinical exacerbations (12). Another study has suggested that inhaled corticosteroids may attenuate airway hyperresponsiveness and also reduce clinical symptoms of COPD, including dyspnea and cough (13). Because these clinical and physiologic markers are also associated with COPD outcomes, inhaled corticosteroids might be expected to decrease COPD-related hospitalizations and mortality.

One approach to ascertaining these outcomes is to use a large population-based cohort focusing in on patients at a very high risk of such events (14, 15). We therefore conducted a large observational study to determine the relationship between use of inhaled corticosteroids and rate of repeat hospitalization and mortality in elderly patients with COPD recently hospitalized for their disease.

METHODS

Data Sources

The details of the cohort of patients used in this study are published elsewhere (16). In brief, we used the Ontario version of the Canadian Institute for Health Information (CIHI) hospital discharge database to identify all Ontario residents with a most responsible discharge diagnosis of COPD between April 1, 1992 and March 31, 1997. Patients were identified using the *International Classification of Diseases, 9th Revision. Clinical Modification* (ICD-9-CM) codes 490.x ("bronchitis not specified as acute or chronic"), 491.x ("chronic bronchitis"), 492.x ("emphysema"), and 496.x ("chronic airways obstruction, not elsewhere classified") (17). This was possible because Ontario provides universal health care coverage for all its residents, regardless of their ability to pay. The validity for using the CIHI data for COPD diagnosis has been demonstrated previously (18). We restricted our cohort to those $\geq$ 65 yr of age in order to minimize the potential diagnostic misclassification between COPD and other chronic obstructive airway diseases that may clinically mimic COPD (19).

We then determined the prescription medications used by this cohort of patients for the same period of time from the Ontario Drug Benefit (ODB) database. This was possible because ODB provided prescription medications free of charge to Ontario residents $\geq$ 65 yr of age. For this study, we searched for inhaled corticosteroids (beclomethasone, budesonide, triamcinolone, and flunisolide), β_2-adrenergics, ipratropium bromide, oral theophyllines, oral corticosteroids and commonly used oral antimicrobials (amoxicillin, sulfa drugs, cephalosporins, quinolones, tetracyline, and macrolides).

We determined use of emergency and outpatient office visits in the preceding year before the index hospitalization for the study patients through the physicians' claims database. Mortality information was

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obtained through the Ontario Registered Persons database, which captures all decedents of Ontario, including their date of death.

Study Design

We used a longitudinal cohort design for this study. We defined the index hospitalization date as the patient's first admission to an acute care hospital between April 1, 1992 and March 31, 1997 with a most responsible diagnosis of COPD. The index discharge date was defined as the date on which patients were discharged from the index hospitalization. We excluded patients who died within 30 d of the discharge date to permit a reasonable window of opportunity for all patients to receive inhaled corticosteroids. We also excluded patients who were transferred to a chronic or another acute-care hospital because outpatient drug information was not available for these patients. The beginning of patient observation time was defined as the date of discharge from the index hospitalization. The end of patient observation time was defined as the first repeat hospitalization for COPD, all-cause mortality, 365 d after discharge from the index admission, or the end of the study period (March 31, 1998), whichever was earliest. March 31, 1998 was used as the end of the study period to ensure that all patients in the cohort had a potential for 1 yr of observation time. We chose a relatively short follow-up time in order to minimize the effects of exposure misclassification (i.e., crossover of nonusers of inhaled corticosteroids to users later on). Moreover, the short follow-up time increased the probability that deaths occurring among the cohort were COPD-related (20). Person-time and COPD hospitalizations occurring after the first repeat hospitalization were censored. Failure was defined as a repeat hospitalization for COPD or death.

Outcome Variables

The main outcome of interest was the relationship between inhaled corticosteroid treatment at or near the index discharge date (within 90 d of the discharge date) and the relative risk (RR) of death or repeat hospitalization for COPD, after adjusting for other important covariates. Repeat hospitalizations for COPD and all-cause mortality were also analyzed separately.

Severity of Disease and Comorbidities

Comorbidities were determined using the CIHI database. A Charlson Index score (21), modified for use in administrative databases (22), was calculated for each individual patient, using ICD-9 CM codes in the 15 secondary diagnosis field. As there may be confounding by indication, we used the following surrogate markers to adjust for disease severity: (*1*) receipt of other airways medications (inhaled β_2-agonists and anticholinergics, oral corticosteroids, and theophylline derivatives) and oral antimicrobials within 90 d of the index discharge date; (*2*) use of emergency room and outpatient physician services for COPD or asthma within 1 yr prior to the index hospitalization date.

TABLE 1. CHARACTERISTICS OF ELDERLY PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE WHO WERE OR WERE NOT TREATED WITH INHALED CORTICOSTEROIDS AFTER DISCHARGE

	No Inhaled Steroids (*n*) (%)	Inhaled Steroids (*n*) (%)	p Value
Patients, n	11,139 (49.2)	11,481 (50.8)	—
Age, yr*	75.5 ± 6.8	74.7 ± 6.5	0.001
Male sex	6,287 (56.4)	6,483 (56.5)	0.969
Charlson Index Score*	0.7 ± 1.1	0.6 ± 0.9	0.001
⩾ 1 dispensing of medications within 90 d of discharge			
Inhaled β_2-adrenergics	5,407 (48.5)	10,311 (89.8)	0.001
Inhaled anticholinergics	3,998 (35.9)	7,828 (68.2)	0.001
Oral corticosteroids	2,600 (23.3)	4,193 (36.5)	0.001
Oral antimicrobials	4108 (36.9)	5,605 (48.8)	0.001
Oral theophyllines	1,575 (14.1)	2,603 (22.7)	0.001
Events occurring within 1 yr prior to hospitalization, n			
Emergency visit*	1.2 ± 1.3	1.6 ± 1.3	0.001
Office visit*	4.1 ± 2.4	4.1 ± 2.3	0.535

* Values are mean ± SD.

Statistical Analyses

The means and standard deviations of continuous variables were compared using Student's two-tailed *t* test. Nonnormally distributed variables were compared using Wilcoxon's Rank Sum test. Ordinal and binary variables were compared using a χ^2 test. Survival rates between patients receiving and not receiving inhaled corticosteroids were compared using the Cox proportional hazards model in order to control for differences in follow-up time and to adjust for the effects of important covariates, including age, sex, modified Charlson comorbidity score, use of various anti-COPD medications listed above, and history of any emergency or office visit for COPD within the previous year of the index hospitalization date. We forced all of these variables in the final model because they have been demonstrated previously to be important determinants of outcomes in COPD (20, 23, 24). All statistical tests were two tailed in nature and a p value < 0.05 was considered statistically significant.

RESULTS

There were 22,620 patients who met the inclusion criteria. There were 5,654 (25.0%) patients who had a repeat hospitalization for COPD and 2,455 (11%) who died during the follow-up period. There were 11,481 (51%) patients with COPD who filled at least one prescription for an inhaled corticosteroid in the first 90 d after the index discharge date. The mean age of those using inhaled corticosteroids postdischarge was 74.7 ± 6.5 yr; 57% of these patients were men. On average, these patients had 4.14 office visits for COPD in the year prior to their hospitalization.

Those using inhaled corticosteroids were slightly younger and less likely to have comorbidity but were more likely to have had an emergency visit for their COPD in the preceding year. Compared with those not receiving inhaled corticosteroids, users had greater utilization of all other anti-COPD medications; inhaled beta-adrenergics, ipratropium bromide, oral corticosteroids, antimicrobials, and theophylline products (Table 1).

In a crude analysis, patients receiving inhaled corticosteroids were 10% (95% confidence interval [CI], 6 to 15%) less likely to have failure within 1 yr than were those not receiving inhaled corticosteroids. After simultaneously adjusting for other covariates, patients who received inhaled corticosteroids had a combined 26% lower adjusted relative risk (RR), 0.74; 95% CI, 0.71 to 0.78%) for repeat hospitalization or death than were those who did not receive inhaled corticosteroids (Figure 1). The RR reduction for all-cause mortality was 29% (95% CI, 22 to 35%), and for repeat hospitalization was 24% (95% CI, 20 to 29%) in favor of those who used inhaled corti-

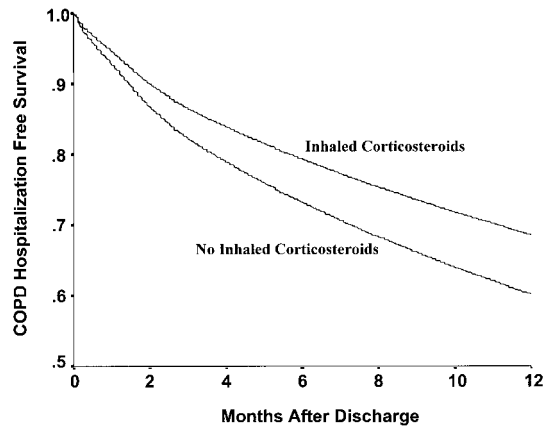

Figure 1. Adjusted probability of hospitalization-free survival in patients with chronic obstructive pulmonary disease who did and did not receive inhaled corticosteroids postdischarge (within 90 d of discharge).

TABLE 2. ADJUSTED RISK OF VARIOUS ANTI-COPD MEDICATIONS RECEIVED WITHIN 90-DAYS POSTDISCHARGE ON ALL-CAUSE MORTALITY AND REPEAT HOSPITALIZATION FOR COPD*

Medications	Mortality RR (95% CI)	Readmission RR (95% CI)
Inhaled corticosteroids	0.71 (0.65 to 0.78)	0.76 (0.71 to 0.80)
β_2 adrenergics	1.00 (0.90 to 1.12)	1.00 (0.97 to 1.01)
Ipratropium bromide	1.00 (0.90 to 1.11)	1.02 (0.96 to 1.10)
Oral theophyllines	1.01 (0.90 to 1.12)	1.20 (1.2 to 1.27)
Antimicrobials	1.08 (0.99 to 1.17)	1.17 (1.10 to 1.23)
Oral corticosteroids	1.37 (1.25 to 1.50)	2.09 (1.97 to 2.20)

Definition of abbreviations: CI = confidence interval; RR = relative risk.

*All relative risks were adjusted for age, sex, Charlson comorbidity score, history of any previous emergency and office visits for COPD, and use of all the other anti-COPD medications listed above. For each cell, the reference category was absence of receipt of the medication.

costeroids. In contrast, receipt of inhaled β-adrenergics, or ipratropium bromide was not associated with mortality or repeat COPD hospitalization. Although both oral theophyllines and antimicrobials were not associated with mortality, they were weakly associated with repeat COPD hospitalization. Oral corticosteroids increased the risk for both mortality and hospitalization (Table 2).

To test the robustness of our analyses, a series of stratified analyses was conducted. The relationship between inhaled corticosteroids and all-cause mortality and repeat hospitalization was similar between patients with and those without comorbidities, as measured by the Charlson comorbidity score (Table 3). Sex also made little difference to this relationship. In men, inhaled corticosteroid therapy was associated with 25% (95% CI, 10 to 30%) fewer failures. In women, we observed 27% (95% CI, 11 to 32%) fewer failures. In those who received ipratropium bromide postdischarge, inhaled corticosteroids were associated with 21% (95% CI, 16 to 26%) fewer failures; 31% (95% CI, 26 to 37%) fewer failures for patients who did not receive ipratropium postdischarge. Age also did not significantly modify the relationship between inhaled corticosteroids and either mortality or repeat hospitalization (Table 4).

DISCUSSION

The most important finding in our study was that inhaled corticosteroid therapy postdischarge was associated with a 26% relative reduction in the combined risk of all-cause mortality and repeat hospitalization in elderly patients with a recent COPD hospitalization. The relative risk reduction for all-cause mortality was 29% (95% CI, 22 to 35%) and for repeat hospitalization was 24% (95% CI, 22 to 35%) in favor of those who used inhaled corticosteroids. Taken together, these data support the use of inhaled corticosteroids for elderly patients with COPD with previous hospitalization for their disease.

Our findings should be placed in the context of previously reported studies. Several earlier studies have suggested that inhaled corticosteroids may reduce airway hyperresponsiveness (25), decrease the rate of decline in lung function (26), improve patient symptoms (27), and reduce the risk of exacerbations (26). However, although these findings were promising, they were not definitive because these studies did not clearly distinguish COPD from asthma.

More recently, several large, multicenter randomized controlled trials were conducted to clarify the role of inhaled corticosteroids in COPD (10–13, 28). These trials used very stringent entry criteria to select out patients with "pure" COPD and thereby minimize diagnostic misclassification. The Copenhagen City Lung Study and the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) (10, 11) showed that the rate of decline in expiratory flow volumes did not significantly change over time (10, 11). Similar findings were reported by Paggiaro and coworkers (28), and by the Inhaled Steroid in Obstructive Lung Disease (ISOLDE) group (12), and the Lung Health Study (13), indicating that the rate of decline in expiratory flow volumes are not modified by inhaled corticosteroids in COPD.

Although decline of lung function as measured by FEV_1 is a significant and important determinant of COPD morbidity and mortality, FEV_1 by itself has relatively weak predictive powers for these outcomes (29). Indeed, clinically relevant changes in health status can occur in the absence of discernable effects on lung function (12). Thus, other indices should also be determined in judging the efficacy of inhaled corticosteroids in COPD. Clinical and physiologic indices such as patient symptoms (30), rates of exacerbations (31), patient's health status (32) and airway hyperresponsiveness (33) have also been demonstrated to be important predictors of COPD morbidity and mortality.

Studies by Paggiaro and coworkers (28), and the ISOLDE group (12) have shown that although inhaled corticosteroids do not modify the rate of decline in expiratory flow volumes, they may modify the rate of decline in patients' (disease-specific) health-related quality of life (HRQL) and reduce exacerbation rates in patients with COPD with moderate to severe disease. In the ISOLDE trial, those receiving inhaled corticosteroids were 25% less likely to have a COPD exacerbation and 24% less likely to withdraw from the study because of respiratory problems than were those receiving placebo (12). Inhaled corticosteroids also significantly reduced the rate of decline in (disease-specific) HRQL by approximately 25% (12). More recently the Lung Health Study has shown that patients receiving inhaled corticosteroids have fewer respiratory symptoms and fewer physician visits for respiratory problems than do those receiving placebo (13). There was also a nonsignifi-

TABLE 3. THE RELATIONSHIP BETWEEN INHALED CORTICOSTEROIDS POSTDISCHARGE AND RISK OF FAILURE (MORTALITY OR READMISSION) IN PATIENTS WITH OR WITHOUT COMORBIDITIES*

Charlson Score	Mortality RR (95% CI)	Readmission RR (95% CI)
0 (no comorbidity)	0.65 (0.57 to 0.74)	0.72 (0.67 to 0.78)
1 (comorbidity)	0.74 (0.63 to 0.87)	0.75 (0.67 to 0.84)
⩾ 2 (highest comorbidity)	0.78 (0.65 to 0.93)	0.82 (0.70 to 0.97)

For definition of abbreviations, *see* Table 2.

* All relative risks were adjusted for age, sex, history of any previous emergency and office visits for COPD, and other anti-COPD medications (*see* METHODS). For each cell, the reference category was absence of receipt of inhaled corticosteroids.

TABLE 4. THE RELATIONSHIP BETWEEN INHALED CORTICOSTEROIDS POSTDISCHARGE AND RISK OF FAILURE (MORTALITY OR READMISSION) IN COPD ACROSS AGE CATEGORIES*

Age, yr	Mortality RR (95% CI)	Readmission RR (95% CI)
65 to 74	0.67 (0.59 to 0.78)	0.74 (0.69 to 0.80)
75 to 84	0.69 (0.60 to 0.79)	0.71 (0.65 to 0.78)
85 and older	0.86 (0.67 to 1.10)	0.84 (0.67 to 1.04)

For definition of abbreviations, *see* Table 2.

* All relative risks were adjusted for sex, Charlson comorbidity score, history of any previous emergency and office visits for COPD, and other anti-COPD medications (*see* METHODS). For each cell, the reference category was absence of receipt of inhaled corticosteroids within 90 d postdischarge.

cant trend towards decreased number of hospitalizations in favor of inhaled corticosteroids (13). Importantly, those receiving inhaled corticosteroids demonstrated lower airway hyperresponsiveness, which has been associated with decreased mortality in COPD (33). We extend these findings by demonstrating that inhaled corticosteroid therapy may also reduce the hospitalization rate and extend survival in patients with COPD.

Dissimilar to our current findings, prior studies (10–13, 28) of inhaled corticosteroids did not show a clear survival advantage with the use of inhaled corticosteroids. However, these latter studies were conducted mostly in patients with only mild to moderate disease, preventing sufficient accrual of mortality data. In contrast, by following a very large group of patients with COPD with a recent hospitalization, our study had sufficient power to evaluate potential survival benefits of inhaled corticosteroids. Moreover, our study focused on the elderly population with very severe disease. Interestingly, the randomized controlled trial that showed the greatest beneficial impact of inhaled corticosteroids on patient outcomes was from Paggiaro and coworkers (28), who studied the oldest of these patients, suggesting that older (i.e $\geqslant$ 65 yr of age) and sicker patients might benefit the most from these medications.

In our study, we observed that use of oral corticosteroids was associated with an increase in mortality and rehospitalization, whereas use of antibiotics was associated with a slightly increased risk of rehospitalizations. Because patients with increased COPD severity receive these medications, these data might reflect confounding by indication (34). However, on the basis of our data, we cannot discount the possibility that because of their systemic side effects, these medications, particularly oral corticosteroids, may cause poor outcomes for patients with COPD (35).

A limitation of this study is the possibility of confounding by indication (36). If patients receiving inhaled corticosteroids had greater disease severity than did those not receiving these medications, significant confounding could be present. There are several pieces of indirect evidence to suggest that this was not the case. Increased utilization of emergency services generally indicates greater disease severity not less (37). In our study, users of inhaled corticosteroids had a greater number of emergency visits for COPD prior to their index hospitalization than did nonusers. In addition, users of inhaled corticosteroids had greater use of other anti-COPD medications, including β_2-adrenergics, oral corticosteroids, and theophyllines. Increased utilization of these medications usually signals greater disease severity and poorer symptom control (38). Indeed, these medications, particularly oral corticosteroids, have been used as surrogate markers for disease severity in other studies (39, 40).

Another concern is the possibility of diagnostic misclassification. Because inhaled corticosteroids are well established for the management of asthma, it is conceivable that those treated with these medications had a significant "asthmatic" component, whereas those not treated had a predominance of emphysema, which portends a worse prognosis (41). In a study by Jackevicius and coworkers (42), in which they audited hospital charts in Ontario, they observed that 48% of patients with unstable COPD were receiving inhaled corticosteroids compared with 56% of unstable asthmatics, a difference that did not reach statistical significance. Although physicians conceptually distinguish asthma and COPD, in their clinical practice, they prescribe similar medications because airflow obstruction and airway inflammation are common to both conditions (43).

We also do not believe that differences in comorbidity or age accounted for our findings. Stratified analysis based on the Charlson comorbidity score (20), a validated instrument for measuring comorbidity with administrative databases (21), and age did not materially modify the relationship between inhaled corticosteroids and either mortality or repeat hospitalization. In our study, we controlled for the three most important factors in predicting morbidity and mortality, age, sex, and comorbidity in COPD (44) and still observed a beneficial effect of inhaled corticosteroids in COPD, suggesting that our results were not spurious.

Observational studies such as this one are not intended to replace well-conducted randomized controlled trials since the former are more susceptible to biases (36). Nevertheless, the former can be a powerful tool for understanding the 'real-life' effectiveness of certain interventions when proper design and methods are applied, particularly for groups of patients who are generally excluded from large trials such as the aged and women (45). Moreover, despite the limitations of observational studies, emerging evidence suggests that their findings for pharmacologic interventions are usually similar to those of large randomized controlled trials (14, 15).

Morbidity and mortality related to COPD have increased worldwide over the last two decades (2), and they represent an important source of resource allocation (1). The present study has suggested that inhaled corticosteroid therapy can improve survival and reduce hospitalization in elderly patients with moderate to severe COPD beyond that achieved by standard pharmacologic therapy. The findings of this study, although not definitive, are consistent with those from other studies (12, 28) and provide a compelling rationale for the conduct of a large randomized trial to further address this critical issue in pulmonary medicine that will have large worldwide implications for years to come.

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