Low-Dose Inhaled Corticosteroid Therapy and Risk of Emergency Department Visits for Asthma

Don D. Sin, MD, MPH; S. F. Paul Man, MD

Background: Patients who visit the emergency department (ED) because of asthma frequently have a relapse. While the use of inhaled corticosteroids has been demonstrated to improve asthma symptoms and lung function, it is not clear whether their use after discharge from the ED reduces asthma relapse rates.

Objective: To determine whether inhaled corticosteroid therapy reduces ED asthma relapse rates.

Methods: We analyzed ED visit and medication data on patients 5 to 60 years of age who were enrolled in a government-sponsored drug plan and who visited an ED because of asthma between April 1, 1997, and March 31, 1999, in Alberta, Canada (N=1293). Using a Cox proportional hazards model, we determined the relative risk (RR) of relapse ED visits among users and nonusers of inhaled corticosteroids after discharge from the ED. We also compared the RR of relapse ED visits across different dose categories.

Results: Users of inhaled corticosteroids after ED discharge had 45% fewer relapse ED visits than did nonusers (adjusted RR, 0.55; 95% confidence interval [CI], 0.44-0.69). Low-, medium-, and high-dose therapies were associated with similar reductions in the risk of relapse ED visits: low-dose therapy (RR, 0.52; 95% CI, 0.39-0.68), medium-dose therapy (RR, 0.51; 95% CI, 0.34-0.76), and high-dose therapy (RR, 0.67; 95% CI, 0.47-0.94).

Conclusions: Inhaled corticosteroid therapy after ED discharge is associated with a significant reduction in the risk of subsequent ED visits. Low-dose therapy appears to be as effective as high-dose therapy. However, further studies are needed to determine the optimal dosing regimen for inhaled corticosteroid therapy for asthma.

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Asthma accounts for nearly 2 million visits to the emergency department (ED) per year, making it the leading cause of ED use among children and young adults in the United States.1 Despite the “best” in-hospital therapy, 30% of these patients will have a relapse within few weeks to months of discharge, leading to recurrent use of EDs for rescue care and necessitating frequent absenteeism from school or work.2 Moreover, once a relapse occurs, the risk of asthma-related morbidity and mortality rises sharply.3

In randomized controlled trials, inhaled corticosteroid therapy has been shown to increase lung function,4 to decrease airway hyperresponsiveness,5 to reduce the need for rescue bronchodilators,6 and to improve asthma symptoms compared with treatment with placebo.6,8 Logically, inhaled corticosteroid therapy should also decrease the risk of subsequent ED visits. However, the use of inhaled corticosteroids after ED discharge remains controversial, as the published studies to date have produced inconsistent and heterogeneous findings.7 The inconsistent findings of published studies may in part be related to small sample sizes and variable follow-up periods among these studies.7 Therefore, more data are needed to determine the utility of these medications among patients with a recent ED visit for asthma.

Information concerning the effect of different doses of inhaled corticosteroids on asthma exacerbation rates would also be useful. Recent studies suggest that these medications, while efficacious, are also fraught with certain adverse effects, including cataract formation,8,9 glaucoma,10 and bone demineralization,11 which occur in a dose-dependent fashion. Avoidance of high-dose therapy, if it is not associated with better asthma control than low-dose therapy, is desirable. A

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PATIENTS AND METHODS

STUDY POPULATION

We obtained ED discharge abstracts from Alberta Health and Wellness through the Ambulatory Care Classification System database. Information from this database included separations (discharges, hospital admissions, transfers, or deaths) for all persons residing in the province of Alberta. For this study, we included Alberta residents, 5 to 60 years of age, who had at least 1 ED visit with asthma as the most responsible diagnosis from April 1, 1997, to March 31, 1999. International Classification of Diseases, Ninth Revision, Clinical Modification, codes 493.0, 493.1, and 493.9 were used to identify these patients. We chose this age cutoff to increase the diagnostic accuracy of the study cohort. We further refined the study cohort by including only patients who were enrolled in the government-sponsored supplementary (nongroup) drug plan, as medication data were available only for those residents. This group was composed mainly of individuals (and their immediate family members) who were self-employed or those who did not have supplementary drug coverage with their employer. We excluded those who died during the first (index) ED visit or during the same hospitalization as part of the index visit. We censored all ED visits that occurred after the first ED visit for each study patient to avoid double counting of patients.

MEDICATION DATA

We merged the Ambulatory Care Classification System database with the Alberta Blue Cross database to obtain information on medications prescribed for the study cohort. All claims in this database contain a unique identification number of the medication, as well as the quantity of drugs and the date dispensed. For each study patient, we determined the use of all asthma medications (short-acting β₂-agonists, ipratropium bromide, inhaled and oral corticosteroids, and oral theophyllines) from April 1, 1997, to March 31, 2001. All medications received before the patient’s index ED visit were censored.

STUDY DESIGN

We followed up our study patients from the date of their first ED visit for asthma to the date of a subsequent ED visit, or to March 31, 2001, whichever came first. This ensured that all study patients had at least 2 years of potential follow-up from their index ED visit. We considered a subsequent ED visit as one in which asthma was the primary diagnosis for the visit.

Because Alberta Blue Cross provides data on the quantity of medications dispensed rather than the daily dose, we imputed the average daily dose of inhaled corticosteroids by using the following method: We first converted all formulations of inhaled corticosteroids into beclomethasone dipropionate equivalents based on equivalency calculations suggested by the Canadian Asthma Consensus Report (Table 1). We then calculated the total dose of the first dispensing of inhaled corticosteroids obtained by patients after their index ED visit. We divided this sum by the elapsed number of days between the first and second dispensings of these medications. For example, if a patient received 1 canister of budesonide (200 µg per puff) containing 200 actuations during the first pharmacy visit after the index ED visit, and if he or she did not refill the next prescription for another 100 days, then the estimated average daily dose for this patient was 500 µg/d. Based on this method, we categorized the patients in our cohort into 5 mutually exclusive inhaled corticosteroid categories: not dispensed, low dose (≤500 µg/d of beclomethasone dipropionate or equivalent), medium dose (501-1000 µg/d), high dose (>1000 µg/d), and indeterminate dose. The latter category included patients who received only 1 dispensing of inhaled corticosteroids and, as such, we could not estimate the daily dose of inhaled corticosteroids consumed by these patients. This method of imputing average daily doses of medications has been used previously.

OTHER FACTORS

Comorbidities were determined using the Ambulatory Care Classification System database. A modified Charlson comorbidity score was calculated for each individual patient, using International Classification of Diseases, Ninth Revision, Clinical Modification, codes in the 15 secondary-diagnosis fields. A Charlson comorbidity score of 0 denotes the absence of any comorbidities; a higher number indicates an increasing burden of comorbidities.

STATISTICAL ANALYSIS

The means and SDs of continuous variables were compared using t tests. Ordinal and binary variables were compared using a χ² test.

We defined inhaled corticosteroid users as patients who were receiving low-, medium-, or high-dose therapy. Nonusers were patients who did not receive any inhaled corticosteroid therapy during the follow-up period. Emergency department visit rates between users and nonusers during the follow-up period were compared using the Cox proportional hazards model. In this model, we controlled for age, sex, Charlson comorbidity scores, whether patients were hospitalized or discharged (home) from their index ED, and use of other asthma medications (within the first 100 days of the index ED visit). We chose a 100-day frame because, in Alberta, pharmacies can fill prescriptions for a maximum period of 100 days. We also used a Cox proportional hazards model (with the same covariates) to determine the relationship between the average daily doses and the risk of a subsequent ED visit in our cohort of patients.

All analyses were conducted with SAS software (Version 8.1; SAS Inc, Carey, NC). All tests were 2-tailed, and P values of less than .05 were considered.
charge is associated with a lower risk for subsequent visits to the ED. We also sought to compare ED relapse rates among patients receiving low-, medium-, and high-dose therapies.

**RESULTS**

**STUDY POPULATION**

We identified 1293 patients between 5 and 60 years of age who had at least 1 ED visit for their asthma during the study period. Of these patients, 499 (38.6%) were men, and 156 (12.2%) were hospitalized during the index ED visit. Only 20 (1.5%) patients had a Charlson comorbidity score of 1 or more. The mean ± SD age of the cohort was 30.8 ± 17.7 years.

**INHALED CORTICOSTEROID USE**

Overall, 658 patients (50.9%) did not receive any inhaled corticosteroids during the follow-up period; 241 (18.6%) received low-dose therapy; 96 (7.4%) received medium-dose therapy; and 122 (9.4%) received high-dose therapy. We could not calculate an average daily dose for 176 patients (13.6%) because they received only 1 dispensing of inhaled corticosteroids during the follow-up period. The baseline characteristics of those who did and did not receive inhaled corticosteroids after ED discharge are shown in Table 2. Users of inhaled corticosteroids were older and more likely to have received other asthma medications, including oral corticosteroids, theophyllines, and ipratropium, during the first 100 days of follow-up. Since these medications are generally reserved for treating those with moderate to severe disease, it is likely that users of inhaled corticosteroids had greater disease severity than nonusers.

**RISK OF SUBSEQUENT ED VISITS**

During the follow-up period, 462 patients (35.7%) had a subsequent ED visit for asthma. Crudely, inhaled corticosteroids were associated with a 36% (relative risk [RR], 0.64; 95% confidence interval [CI], 0.52-0.79) reduction in the risk for a subsequent ED visit. After adjustment for all factors in our model, users of inhaled corticosteroids after ED discharge had a 45% (RR, 0.55; 95% CI, 0.44-0.69) reduction in the risk for a subsequent ED visit compared with nonusers of inhaled corticosteroids (Figure). Patients who received low-dose therapy had 48% (RR 0.52; 95% CI, 0.39-0.68) fewer subsequent ED emergency visits compared to nonusers. Those receiving medium- and high-dose therapy also had fewer subsequent ED visits (RR for medium dose, 0.51; 95% CI, 0.34-0.76; RR for high-dose 0.67; 95% CI, 0.47-0.94). Those in the indeterminate-dose group did not experience any significant changes in their risk for subsequent ED visits compared with nonusers (RR, 1.01; 95% CI, 0.78-1.32) (Table 3).

To determine the robustness of the relationship between inhaled corticosteroid therapy and risk of a subsequent ED visit, we conducted a series of subgroup analyses. Among those who received at least 1 dispensing of a bronchodilator (ie, β₂-adrenergics, ipratropium, or oral

<table>
<thead>
<tr>
<th>Inhaled Corticosteroids</th>
<th>Conversion Factor to Bepremethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Budesonide (Turbuhaler®)</td>
<td>1.25</td>
</tr>
<tr>
<td>Budesonide (for nebulization)</td>
<td>0.50</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>2.00</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>0.50</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*A dry-powder inhaler.

**Table 2. Characteristics of Patients With Asthma Stratified According to Use (or Nonuse) of Inhaled Corticosteroids**

<table>
<thead>
<tr>
<th>No Inhaled Corticosteroids</th>
<th>Inhaled Corticosteroids</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>28.9 ± 16.7</td>
<td>32.8 ± 18.5</td>
</tr>
<tr>
<td>5-14</td>
<td>148 (22.5)</td>
<td>154 (24.3)</td>
</tr>
<tr>
<td>15-24</td>
<td>203 (30.9)</td>
<td>108 (17.0)</td>
</tr>
<tr>
<td>25-34</td>
<td>69 (10.5)</td>
<td>68 (10.7)</td>
</tr>
<tr>
<td>35-44</td>
<td>77 (11.7)</td>
<td>79 (12.4)</td>
</tr>
<tr>
<td>≥45</td>
<td>161 (24.5)</td>
<td>226 (35.6)</td>
</tr>
<tr>
<td>Males</td>
<td>245 (37.2)</td>
<td>254 (40.0)</td>
</tr>
<tr>
<td>Hospitalization†</td>
<td>70 (10.6)</td>
<td>88 (13.9)</td>
</tr>
<tr>
<td>β₂-Adrenergics‡</td>
<td>432 (65.7)</td>
<td>506 (79.7)</td>
</tr>
<tr>
<td>Ipratropium bromide‡</td>
<td>43 (6.5)</td>
<td>74 (11.7)</td>
</tr>
<tr>
<td>Oral theophyllines‡</td>
<td>35 (5.3)</td>
<td>70 (11.0)</td>
</tr>
<tr>
<td>Oral corticosteroids‡</td>
<td>159 (24.2)</td>
<td>243 (38.3)</td>
</tr>
<tr>
<td>Charlson index ≥1</td>
<td>5 (0.8)</td>
<td>15 (2.4)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate percentage of column total unless otherwise stated; ellipses, not applicable.
†Hospitalization resulting from the index emergency department visit.
‡Medication use reflects at least 1 dispensing within the first 100 days after discharge.
demonstrate. Because prior research has focused on less important outcomes such as ED readmission rates that impact of inhaled corticosteroid therapy on clinically 2-year follow-up period.

Rates of subsequent ED visits were similar among low-, medium-, and high-dose therapy groups over a permissions in airway hyperresponsiveness but no appreciable benefits on asthma symptoms or exacerbation rates with high-dose therapy (over low-dose therapy).12

Because our study is observational in nature, relying on information from administrative databases, confounding by indication is of concern. However, users and nonusers of inhaled corticosteroids had similar rates of hospitalization for their asthma (Table 2), suggesting that there were no significant dissimilarities in disease severity between these 2 groups. Moreover, users of inhaled corticosteroids were more likely to be using bronchodilators and oral corticosteroids after discharge from the ED than nonusers. Since these medications are markers of increased asthma severity,21,22 it is highly unlikely that confounding by indication could explain away our findings.

Based on our data, we cannot be certain on what the “optimal” dose of inhaled corticosteroids ought to be. However, they do provide some assurances for the practicing clinicians that in most cases low-dose inhaled corticosteroid therapy could be used for long-term asthma control in patients who have recently been discharged from EDs. Future randomized trials are required to confirm our findings and to determine “best” doses of inhaled corticosteroids for reducing asthma-related morbidity and mortality in this high-risk group of patients.

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Theophylline), users of inhaled corticosteroids were 45% less likely to experience a subsequent ED visit than nonusers (RR, 0.55; 95% CI, 0.43-0.70). In this sub- sample size and comprehensive follow-up of patients, we were able to explore a dose-response relationship between the use of inhaled corticosteroids and ED relapse rates. In the absence of clear clinical data, some physicians may believe that “more is better” when it comes to the use of inhaled corticosteroids in asthma. Our data, on the other hand, suggest that even low doses are effective in lowering ED relapse rates among persons with asthma.

Our findings are consistent with those of Hummel and Lehtonen,20 who showed that high-dose therapy offered no significant advantages over low-dose therapy in reducing asthma symptoms, in the use of on-demand rescue medications, or in improvement of lung function. These results have been further supported by a recent meta-analysis that demonstrated only marginal improvements in airway hyperresponsiveness but no appreciable benefits on asthma symptoms or exacerbation rates with high-dose therapy (over low-dose therapy).12

Theophyllines), users of inhaled corticosteroids were 45% less likely to experience a subsequent ED visit than nonusers (RR, 0.55; 95% CI, 0.43-0.70). In this sub- group of patients, low- (RR, 0.53; 95% CI, 0.39-0.72), medium- (RR, 0.48; 0.31-0.74), and high- (RR, 0.67; 95% CI, 0.46-0.98) dose therapy were all associated with significant reductions in the risk for subsequent ED visits. A similar pattern was observed when we restricted the analysis to patients who received oral corticosteroid therapy within the first 100 days of the index ED visit. We found that low- (RR, 0.41; 95% CI, 0.26-0.64), medium- (RR, 0.46; 95% CI, 0.25-0.85), and high- (RR, 0.55; 95% CI, 0.34-0.88) dose therapy were all associated with significant reductions in the risk for subsequent ED visits.

Since inhaled corticosteroid therapy before the index ED visit could be a marker of more severe disease, we performed a subgroup analysis in patients who did not receive any inhaled corticosteroids within 200 days before the index ED date. In this “steroid-naive” group (n=975), those who received these medications after ED discharge had 49% fewer subsequent ED visits than the nonusers (RR, 0.51; 95% CI, 0.32-0.76). Low, medium, and high doses were associated with a 51% (RR, 0.49; 95% CI, 0.34-0.71), 44% (RR, 0.56; 95% CI, 0.34-0.92), and 48% (RR, 0.52; 95% CI, 0.31-0.89) reduction in the risk for ED readmissions, respectively, in this subgroup of patients. Similar findings were present in those who had used inhaled corticosteroids before the index ED date (RR, 0.49; 95% CI, 0.39-0.68).

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Table 3. Relationship Between Subsequent Emergency Department (ED) Visits and Inhaled Corticosteroid Therapy

<table>
<thead>
<tr>
<th>Inhaled Corticosteroids</th>
<th>Total No. of Patients</th>
<th>Subsequent ED Visits, No. (%)</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not dispensed</td>
<td>658</td>
<td>256 (38.9)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>176</td>
<td>75 (42.6)</td>
<td>1.01 (0.78-1.32)</td>
</tr>
<tr>
<td>Low dose</td>
<td>241</td>
<td>63 (26.1)</td>
<td>0.52 (0.39-0.68)</td>
</tr>
<tr>
<td>Medium dose</td>
<td>96</td>
<td>27 (28.1)</td>
<td>0.51 (0.34-0.76)</td>
</tr>
<tr>
<td>High dose</td>
<td>122</td>
<td>41 (33.6)</td>
<td>0.67 (0.47-0.94)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, use of antiasthma medications, comorbidities, and hospitalization (see “Patients and Methods” section for details). RR indicates risk ratio; CI, confidence interval.

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