Risk of Adverse Gastrointestinal Events from Inhaled Corticosteroids

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Study Objective. To determine whether patients prescribed inhaled corticosteroids are at risk for adverse gastrointestinal effects.

Design. Retrospective cohort study.

Setting. Urban health center with an academic affiliation.

Patients. A total of 19,443 adults (mean age 31.8 yrs) with airways disease, defined as a diagnosis of asthma or chronic obstructive pulmonary disease, and who were prescribed both an inhaled corticosteroid and albuterol (7156 patients) or inhaled albuterol alone (12,287 patients) between November 1977 and February 2002.

Measurements and Main Results. The frequency of adverse gastrointestinal events in the patients who used inhaled corticosteroids and albuterol was compared with that in the patients who used albuterol alone. Adverse gastrointestinal outcomes included events such as gastritis, ulcers, and bleeding. Cox proportional hazards models were used to determine the risk of adverse events, controlling for possible confounders such as alcohol use or nonsteroidal antiinflammatory drug use. Adverse gastrointestinal events were observed in 461 (6.4%) patients using inhaled corticosteroids and albuterol and in 302 (2.5%) patients using only albuterol. After controlling for potential confounders, patients who used inhaled corticosteroids and albuterol had an increased risk for adverse gastrointestinal events compared with patients who used only inhaled albuterol (hazard ratio [HR] 1.26, 95% confidence interval [CI] 1.02–1.56). A prescription for a spacer device reduced this risk among patients using an inhaled corticosteroid (HR 0.26, 95% CI 0.20–0.34).

Conclusion. Patients using inhaled corticosteroids appear to have a slight risk for adverse gastrointestinal events that is mitigated in patients who used a spacer device.

Key Words: inhaled corticosteroids, gastrointestinal adverse events, spacer, obstructive airways disease, asthma.

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Inhaled corticosteroids are commonly used to treat obstructive airways diseases including asthma and chronic obstructive pulmonary disease (COPD). For asthma, inhaled corticosteroids are the primary treatment of underlying airway inflammation and have been shown to reduce morbidity, mortality, and the costs of health care.[1–5] Inhaled corticosteroids also are used in treating patients with COPD, although the benefits are less well confirmed.[6-8] For both asthma and COPD, inhaled corticosteroids are preferred over oral corticosteroids for long-term treatment because they produce high levels of topical antiinflammatory activity and low levels of systemic activity.[9, 10] Although inhaled corticosteroids are relatively safe and effective, adverse effects may occur in patients receiving long-term treatment. Documented adverse effects

include adrenal suppression,[11–13] osteoporosis in adults[14, 15] or reduced growth rates in children,[16] cataracts,[17–20] glaucoma,[21, 22] and dermal thinning.[23–25]

Although evidence is conflicting, gastrointestinal complications such as ulcers and bleeding may occur in patients treated with long-term oral corticosteroids. For example, a pooled analysis of 71 controlled trials revealed a risk of gastrointestinal events with oral corticosteroids.[26] Similarly, a case-control study of Medicaid data found an increased risk of gastrointestinal events with corticosteroids but also found that it was primarily restricted to patients treated with nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids concomitantly.[27] An analysis of the United Kingdom General Practice Research Database confirmed the additional risk associated with concomitant NSAID administration, although this study also found monotherapy with oral corticosteroids to pose significant risk of gastrointestinal adverse events.[28]

Despite somewhat contradictory evidence, oral corticosteroids appear to have some degree of heightened risk for adverse gastrointestinal events. Previous evidence suggests that inhaled corticosteroids are not associated with gastrointestinal adverse events,[29, 30] even though studies have indicated that inhaled corticosteroids produce systemic effects, and there is some degree of gastric exposure with inhaled products.[11–25] Therefore, we conducted an exploratory analysis to ascertain whether inhaled corticosteroids are associated with gastrointestinal adverse events.

Methods

Patient Population

This study was approved by the Indiana University–Purdue University institutional review board. All patients included in the study received their medical care and drug therapy from Wishard Health Services (Indianapolis, IN) between November 1977 and February 2002. During this time frame, we identified patients who were at least 18 years old, had airways disease defined as a diagnosis of asthma or COPD, and had at least one prescription for the sympathomimetic β_2-adrenergic agonist albuterol or for both an inhaled corticosteroid and albuterol. Only patients who had at least one clinic visit 6 months before their first prescription for an inhaled corticosteroid or albuterol were included. We excluded patients with any evidence documented in their automated medical records of an adverse gastrointestinal event, such as gastritis, gastrointestinal bleed, ulcer, or esophagitis, during the 6 months before initiation of an inhaled corticosteroid or albuterol.

Study Design

A retrospective cohort study design was used (Figure 1). Two groups were formed to represent patients treated with an inhaled corticosteroid and a comparison group not prescribed an inhaled corticosteroid. Patients in the inhaled corticosteroid group were those prescribed both an inhaled corticosteroid and albuterol, and patients in the comparison group were prescribed inhaled albuterol only. Because intranasally administered corticosteroids ultimately reach the stomach and duodenum, we also included their use in the inhaled corticosteroid group.

The index date for patients in the corticosteroid cohort was the date of the patient's first prescription for one of the following inhaled corticosteroids: beclomethasone, flunisolide, fluticasone, or triamcinolone. The index date for patients in the albuterol group was the date of the patient's first prescription for albuterol. The inhaled steroids budesonide and mometasone were not on the health system's formulary during the time of this study and thus were not included in our analysis.

Data Source

We used automated data from the Regenstrief Medical Record System (RMRS). Beginning in 1974, the RMRS has been the central repository for clinical data for outpatients and inpatients seeking care at Wishard Health Services, an inner-city medical center in Indianapolis, Indiana. The RMRS is a modular system containing registration and appointment data, prescriptions (including prescriptions for over-

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the-counter products filled through a Wishard pharmacy), and diagnostic data from laboratory, radiology, and endoscopic procedures. Radiologic and endoscopic data include the procedure dates and diagnoses for upper gastrointestinal radiologic examinations and endoscopy.

Prescription data derive from two sources. The first source is an archival database that spans back to 1974 and contains the name of the drug dispensed and the dispensing date. The second source is a prescription module spanning back to 1992 that was created directly from the electronic prescription records and contains virtually all data on each drug dispensed including the physician's instructions for use. In these databases, physicians' orders for spacer devices were stored in the same manner as all other prescriptions. These modules capture both prescription and over-the-counter products, as long as they were provided by the Wishard Health System. During the past decade, two internal surveys of adult outpatients with uncomplicated hypertension, coronary artery disease, heart failure, and obstructive airways disease indicated that patients seen at Wishard receive more than 95% of their prescription and over-the-counter drugs at Wishard Health System pharmacies.[31]

Primary Outcome Measures

The primary end point was incident gastrointestinal ulcer, perforation, or bleeding as diagnosed by a physician or identified by diagnostic procedure (radiology, endoscopy, sigmoidoscopy, or colonoscopy). Qualifying documented diagnoses included any gastrointestinal ulceration, perforation, esophagitis, gastritis, hemorrhage, hematemesis, hematochezia, or melena. We searched for evidence of patients reaching the end point after their index date but before their last prescription for an inhaled corticosteroid (in the inhaled corticosteroid group) or inhaled albuterol (in the albuterol group). For this analysis, we used prescription and end point data for the period November 14, 1977–February 19, 2002.

Statistical Analysis

We followed patients from the index prescription date to end point or censoring. Patients reaching the end point were considered as having experienced an adverse gastrointestinal event; otherwise, follow-up was censored 1 month after their last prescription for an inhaled corticosteroid or albuterol. Observations also were censored with death or when no additional observations

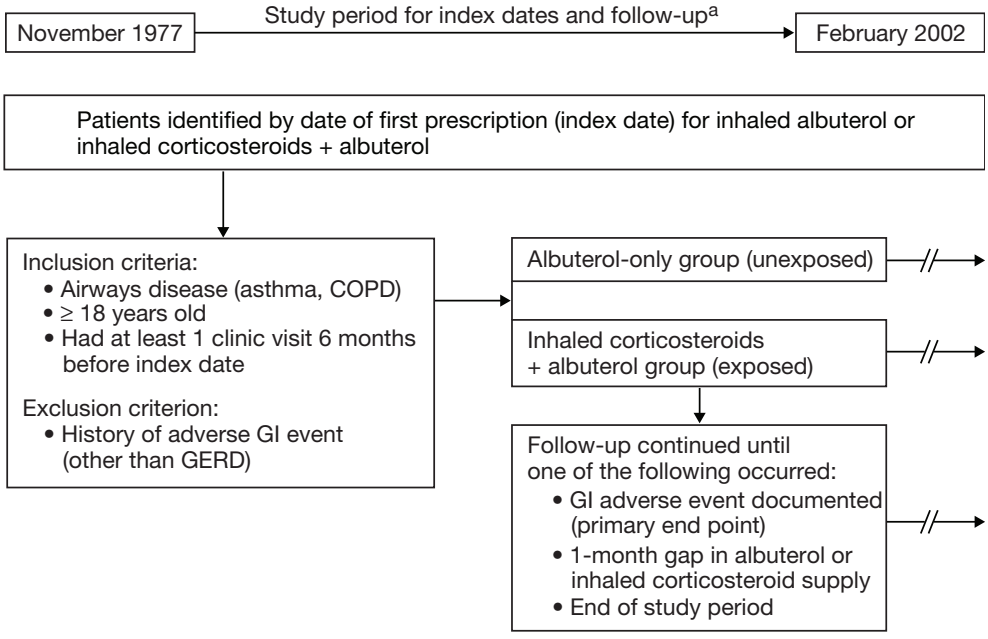

Figure 1. Study design schematic. COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; GI = gastrointestinal. [a]Mean ± SD duration of follow-up was 5.7 ± 3.7 years (range 1–24.3 yrs).

were recorded in the RMRS. The outcome represented the duration from the index prescription to end point or censoring. The distribution of duration from the index date to the event (or censoring) time was quantified by a survival function for each treatment group. Kaplan-Meier curves were used to depict the estimated survival functions of patients in the inhaled corticosteroid and albuterol groups. The method also was used to illustrate the difference in survival experience between inhaled steroid users with and without spacer devices. We conducted subgroup analyses for patients without any evidence of prescriptions for NSAIDs because of previous work suggesting that concomitant NSAID use significantly increases risk with oral steroids.[27, 28]

Cox proportional hazards regression models were used to examine the association between inhaled corticosteroid use and the development of the adverse gastrointestinal end point while controlling for confounders and effect modifiers. These variables included baseline demographics (age, race, sex) and relevant behavioral characteristics (smoking and alcohol use), and comorbidities that could represent diagnostic biases (evidence of oral thrush or gastroesophageal reflux disease). We also assessed the impact of short-term administration of effect-modifying drugs known to have acute gastrointestinal effects that were administered within 6 months before end point or censoring (e.g., short-term administration of oral corticosteroids, iron-containing drugs, NSAIDs, theophylline, and alendronate). We considered other potential effect-modifying drugs such as risedronate and etidronate, but these drugs were not on formulary at the time of this study. Cox regression models were created to adjust for the main effects (e.g., oral corticosteroids) and interaction, such as treatment by NSAIDs, smoking by alcohol use, iron-containing drug use by sex. The final model selected was based on the significance of the model predictors. The adjusted effect of the inhaled corticosteroids was then tested by using the Wald χ^2 test and the magnitudes of effects quantified by the hazard ratios (HRs) of the covariates and their 95% confidence intervals (CIs).

Data from the prescription module of the RMRS from 1992–2002 were used to examine the dose effect—as low, moderate, and high dose—of the inhaled and intranasal corticosteroids. The definition of low, moderate, and high dose was that used by the National Asthma Education and Prevention Program Expert Panel Report.[10] Patients receiving a low-dose inhaled corticosteroid plus an intranasal corticosteroid were elevated to the moderate-dose level, and those receiving a moderate-dose inhaled corticosteroid plus an intranasal corticosteroid were elevated to the high-dose level.

A priori we wished to determine the effect of a spacer device on any observed risk of adverse gastrointestinal events. As such, we conducted additional analyses to gain insights into the effect of spacer use. We evaluated the effect of a prescription for a spacer on the development of adverse gastrointestinal events in all study patients and then restricted our analysis to the inhaled corticosteroid group. Analyses were conducted by using SAS, version 8.2 (SAS Institute, Inc., Cary, NC). Two-sided p values of less than 0.05 were used in statistical inferences.

Results

Patient Characteristics

Of 28,272 patients prescribed an inhaled corticosteroid or albuterol, 8829 patients were excluded because of a history of one of the end point diagnoses before their index prescription date. Of the remaining 19,443 patients, 7156 patients had been prescribed both an inhaled corticosteroid and albuterol and 12,287 patients had been prescribed albuterol alone. Beclomethasone (59.5%) was the most commonly prescribed inhaled corticosteroid followed by fluticasone (24.6%), triamcinolone (13.9%), and flunisolide (2.1%). In the inhaled corticosteroid group, 5695 (79.6%) used only an orally inhaled product and 1461 (20.4%) used both orally and intranasally inhaled products. Patient characteristics of the inhaled corticosteroid and albuterol study groups are shown in Table 1. Patients in the inhaled corticosteroid group were more likely older, female, a smoker, diagnosed with COPD and gastroesophageal reflux disease, and receiving NSAIDs, potassium supplements, oral corticosteroids, and a spacer device ($p<0.001$). The mean ± SD duration of follow-up was 5.7 ± 3.7 years (median 4.8 yrs, range 1–24.3 yrs).

Incident Adverse Gastrointestinal Events

Incident adverse gastrointestinal events were observed in 763 (3.9%) of the 19,443 study patients during the course of observation. Of the 7156 patients in the inhaled corticosteroid group, 461 (6.4%) experienced an event while receiving

Table 1. Demographic and Clinical Characteristics of the Study Patients

Characteristic	Inhaled Corticosteroid + Albuterol (n=7156)	Albuterol Only (n=12,287)	Total (n=19,443)
		Mean ± SD	
Age on index date (yrs)	34.0 ± 18.0	30.5 ± 18.6	31.8 ± 18.5
		No. (%) of Patients	
Women	4709 (65.8)	7151 (58.2)	11,860 (61.0)
African-American	3714 (51.9)	6303 (51.3)	10,017 (51.5)
Asthma	6083 (85.0)	11,181 (91.0)	17,264 (88.8)
COPD	1073 (15.0)	1106 (9.0)	2179 (11.2)
Cigarette smoking	1169 (16.3)	1119 (9.1)	2288 (11.8)
Alcohol use	973 (13.6)	1769 (14.4)	2742 (14.1)
Oral thrush[a]	14 (0.2)	12 (0.1)	26 (0.1)
GERD[a]	651 (9.1)	369 (3.0)	1020 (5.2)
Spacer device[a]	5331 (74.5)	7077 (57.6)	12,408 (63.8)
Concomitant drugs[a]			
Iron-containing drug	372 (5.2)	700 (5.7)	1072 (5.5)
NSAID	2476 (34.6)	3576 (29.1)	6052 (31.1)
Potassium supplement	964 (13.5)	750 (6.1)	1714 (8.8)
Oral corticosteroid	1553 (21.7)	1290 (10.5)	2843 (14.6)
Theophylline	444 (6.2)	491 (4.0)	935 (4.8)
Alendronate	7 (0.1)	12 (0.1)	19 (0.1)

COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; NSAID = nonsteroidal antiinflammatory drug.
[a]Recorded after the index date but within 6 months of the event or censoring date.

an inhaled corticosteroid. The most common events documented in the inhaled corticosteroid group were gastritis in 163 patients (2.3%), gastrointestinal bleed in 152 (2.1%), ulcer in 101 (1.4%), and esophagitis in 45 (0.6%). Of the 12,287 patients in the albuterol group, 302 patients (2.5%) experienced an adverse gastrointestinal event, including gastritis in 91 (0.7%), gastrointestinal bleed in 121 (1.0%), ulcer in 64 (0.5%), and esophagitis in 26 (0.2%). The proportion of patients experiencing a gastrointestinal event was greater in the inhaled corticosteroid group than the albuterol group, regardless of event type ($p<0.05$ for all).

Crude survival function estimates using Kaplan-Meier curves (Figure 2) show the change in hazard function for all patients (panel A) and the probability for patients who had not received an NSAID (panel B). Regardless of NSAID use, patients in the inhaled corticosteroid group experienced greater risk for a gastrointestinal disorder than patients in the albuterol group,

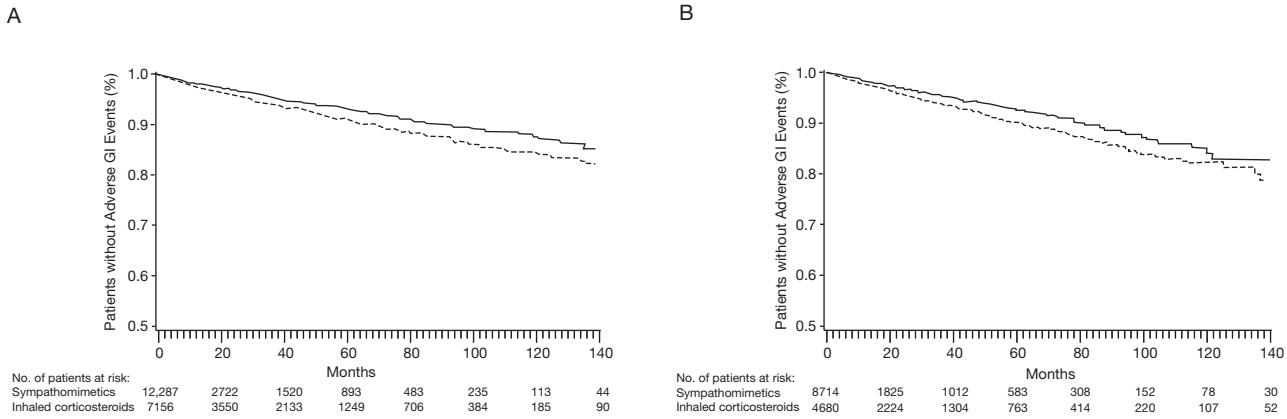

Figure 2. Kaplan-Meier estimates of the percentage of patients in the inhaled corticosteroid group (dashed lines) and albuterol only (sympathomimetics) group (solid lines) without adverse gastrointestinal (GI) events for all patients (panel A) and for patients who had not used nonsteroidal antiinflammatory drugs within 6 months of the event or censoring date (panel B).

Table 2. Results of Multivariable Cox Regression Models Examining the Relationship Between Inhaled Corticosteroid Use and the Risk of Adverse Gastrointestinal Events

	All Patients (n=19,442)		Patients Not Using NSAIDs[a] (n=13,393)	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
Sex (male = 1)	0.98 (0.84–1.15)	0.81	0.90 (0.72–1.12)	0.33
Race (African-American = 1)	0.80 (0.69–0.93)	0.003	0.84 (0.69–1.03)	0.09
Age on index date (yrs)	1.02 (1.02–1.03)	<0.001	1.02 (1.01–1.02)	<0.001
		Yes = 1		
Inhaled corticosteroids	1.27 (1.09–1.48)	0.002	1.26 (1.02–1.56)	0.03
Asthma	0.74 (0.59–0.91)	0.004	0.68 (0.51–0.90)	0.006
Cigarette smoking	1.40 (1.19–1.65)	<0.001	1.40 (1.10–1.77)	0.01
Alcohol use	1.60 (1.36–1.89)	<0.001	1.86 (1.48–2.34)	<0.001
Oral thrush[b]	2.45 (0.78–7.66)	0.13	1.68 (0.23–12.11)	0.61
GERD[b]	1.07 (0.86–1.32)	0.56	1.28 (0.95–1.71)	0.10
Concomitant drugs[b]				
Iron-containing drug	1.55 (1.19–2.01)	0.001	1.45 (0.98–2.14)	0.07
NSAID	1.31 (1.13–1.51)	<0.001	—	—
Potassium supplement	1.27 (1.06–1.52)	0.008	1.16 (0.98–1.52)	0.27
Oral corticosteroid	1.09 (0.90–1.32)	0.36	1.09 (0.84–1.40)	0.52
Spacer device	0.34 (0.30–0.40)	<0.001	0.34 (0.28–0.42)	<0.001
Theophylline	1.43 (1.16–1.75)	<0.001	1.79 (1.36–2.34)	<0.001

NSAID = nonsteroidal antiinflammatory drug; HR = hazard ratio; CI = confidence interval; GERD = gastroesophageal reflux disease.

[a]Patients who were not prescribed NSAIDs within 6 mo before the event or censoring time.

[b]Refers to the time period after the index date but within 6 mo of the event or censored date. One patient was removed from the analyses because of a missing response.

suggesting an association between the use of inhaled corticosteroid and an incident gastrointestinal disorder. However, such graphic representations do not control for other confounders.

Cox regression models further confirmed the finding after controlling for other risk factors and covariates (Table 2). Patients in the inhaled corticosteroid group had a greater risk for adverse gastrointestinal events despite their NSAID status. For all patients, the risk (i.e., HR) of adverse gastrointestinal event was 1.27 (95% CI 1.09–1.48), whereas for those without evidence of NSAID use the risk was 1.26 (95% CI 1.02–1.56). In other words, the risk of a gastrointestinal disorder was approximately 26% greater among patients prescribed an inhaled corticosteroid and albuterol compared with patients prescribed albuterol only. Other significant factors associated with the end point included older age (p<0.001, HR 1.02), asthma (p=0.004, HR 0.74), cigarette smoking (p<0.001, HR 1.40), alcohol use (p<0.001, HR 1.60), and the use of an iron-containing drug (p=0.001, HR 1.55), NSAIDs (p<0.001, HR 1.31), or theophylline (p<0.001, HR 1.43). Of interest, the use of oral corticosteroids was not significant.

We repeated our analyses excluding patients prescribed oral corticosteroids, and the inhaled corticosteroid effect remained significant (data not shown, p=0.02). Moreover, in the subset of patients prescribed inhaled corticosteroids from 1992–2002 (when more detailed data on drug dispensing and directions for use were available), we found that the risk of adverse gastrointestinal event was 3.7% among patients prescribed relatively low doses of inhaled corticosteroid, 4.5% among those prescribed moderate doses, and 8.8% among patients prescribed high doses (p=0.03 for trend).

Effect of Receipt of a Spacer Device

Among all patients, receipt of a spacer (Table 2) had a significant mitigating effect on the risk of adverse gastrointestinal events (p<0.001, HR 0.34). These results imply that the risk of developing the adverse gastrointestinal events among patients prescribed a spacer was 66% lower than that in patients who had not received a spacer.

To assess whether receipt of a spacer reduced the risk of adverse gastrointestinal event rates specifically within the inhaled corticosteroid–treated patients, we compared the Kaplan-Meier estimates of the hazard function of inhaled corticosteroid–treated patients who had been prescribed a spacer with that of patients who had

Table 3. Results of Multivariable Cox Regression Models Examining the Relationship Between Spacer Use and the Risk of Adverse Gastrointestinal Events in Patients Prescribed Inhaled Corticosteroids

	All Patients Using Inhaled Corticosteroids (n=7155)		Patients Using Inhaled Corticosteroids but not NSAIDs[a] (n=4679)	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
Sex (male = 1)	1.03 (0.84–1.27)	0.77	0.92 (0.69–1.23)	0.59
Race (African-American = 1)	0.84 (0.69–1.01)	0.06	0.86 (0.66–1.12)	0.26
Age on index date (yrs)	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	0.002
		Yes = 1		
Spacer device	0.29 (0.24–0.35)	<0.001	0.26 (0.20–0.34)	<0.001
Asthma	0.76 (0.59–0.99)	0.044	0.64 (0.45–0.90)	0.01
Smoking	1.44 (1.17–1.77)	<0.001	1.45 (1.08–1.95)	0.01
Alcohol use	1.53 (1.23–1.91)	<0.001	1.80 (1.33–2.44)	<0.001
Concomitant drugs[b]				
Iron-containing drug	1.62 (1.15–2.28)	0.006	1.67 (1.02–2.71)	0.04
NSAID	1.35 (1.12–1.62)	0.002	—	—
Potassium supplement	1.37 (1.10–1.72)	0.006	1.36 (0.98–1.90)	0.06
Oral corticosteroid	1.24 (0.99–1.54)	0.06	1.23 (0.92–1.65)	0.16
Theophylline	1.47 (1.15–1.88)	0.002	1.80 (1.30–2.49)	<0.001

NSAID = nonsteroidal antiinflammatory drug; HR = hazard ratio; CI = confidence interval

[a]Patients who were using inhaled corticosteroids but were not prescribed NSAIDs within 6 mo of the event or censoring date.

[b]Refers to the time period after index date but within 6 mo of the event or censoring date. One patient was removed from the analyses because of a missing response.

not (Figure 3). The evidence from Figure 3 suggests that receipt of a spacer device is indeed associated with a reduced risk of an adverse gastrointestinal event. Cox regression models further confirmed this observation (Table 3). The HR for receipt of a spacer was 0.29 (95% CI 0.24–0.35) among all patients prescribed inhaled corticosteroids and 0.26 (95% CI 0.20–0.34) among the subset of patients who had not been prescribed an NSAID. The results imply that the risk of adverse gastrointestinal event is 71% less among patients who receive a spacer device compared with those who do not.

Discussion

Our results suggest that patients prescribed inhaled corticosteroids have a slight risk for adverse gastrointestinal events (primarily gastritis), which is mitigated when patients receive a spacer device. Oral corticosteroids have been implicated as a risk factor for adverse gastrointestinal events such as ulcers for many years, but to our knowledge, our study is the first to suggest a possible effect from inhaled corticosteroids.

Although the target of an inhaled corticosteroid is the lung, a considerable amount of the drug

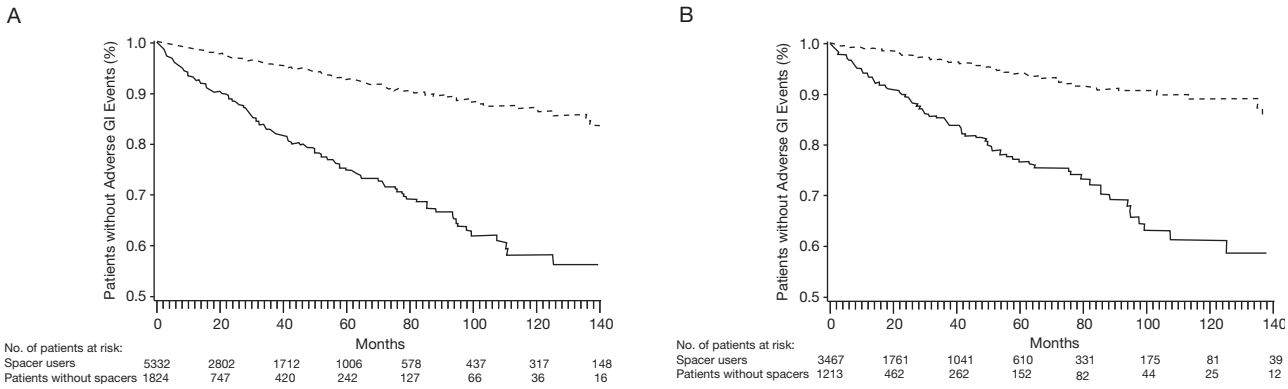

Figure 3. Kaplan-Meier estimates of the percentage of patients prescribed inhaled corticosteroids with a spacer device (dashed lines) and those without spacer use (solid lines) who did not have adverse gastrointestinal (GI) events for all users of inhaled corticosteroids (panel A) and for those who used inhaled corticosteroids but had not used nonsteroidal antiinflammatory drugs within 6 months of the event or censoring date (panel B).

appears in the gastrointestinal tract including the lining of the esophagus, the stomach, intestine, and colon.[32, 33] Scintillation studies have revealed large boluses of radiolabeled drug appearing in the stomach when metered-dose inhalers are used without spacer devices.[34] However, little drug is observed when the spacer device is used with the metered-dose inhaler. Presumably, the reduced amount of inhaled corticosteroid that is swallowed or deposited in the oropharynx and ultimately swallowed reduces the risk of adverse gastrointestinal events such as gastritis, ulceration, and bleeding.

Our findings should be viewed in light of the conflicting evidence from previous studies assessing risk with oral corticosteroids. Although a large meta-analysis indicated a risk of ulceration from oral corticosteroids,[26] this evidence is contradicted by a case-control study that concluded that the increased risk of developing peptic ulcer disease was limited to patients with concurrent NSAID use.[27] In our study, despite NSAID use, we found that patients treated with oral corticosteroids were not at a statistically significant higher risk for developing gastrointestinal adverse events. However, inhaled corticosteroid–treated patients had a greater risk for gastrointestinal adverse events even after controlling for NSAID use. A possible explanation for the association of inhaled but not oral corticosteroids with gastrointestinal adverse events may be related to the intensity or duration of exposure. The average duration of inhaled corticosteroid exposure was roughly 1 year, whereas oral corticosteroid use generally covered a shorter time interval (e.g., median duration 1 mo). Thus, part of the reason we identified a risk of gastrointestinal adverse events with inhaled but not oral corticosteroids could be related to differences in exposure. We measured both short-term bursts and regular use for oral steroids, whereas inhaled steroids were typically administered on a regular basis over longer periods of time. This distinction likely biased our estimate of risk downward for oral steroids. More research is needed to examine how long-term oral corticosteroid use compares with long-term inhaled corticosteroid use.

Limitations

We acknowledge several important limitations of this study. First, we used automated observational data from a large health care system over a long duration assuming that drug use during the interval between first and last prescription represented continuous use of drug. Such practice data may have been collected differently over time, important changes may have occurred with diagnostic instrumentation and procedures, and inhaled corticosteroids have become increasingly potent. These factors could bias our findings. Second, although we were able to account for patient-level variables such as smoking, alcohol use, and over-the-counter drug use—variables often missed in observational studies such as ours—residual confounding could exist and could possibly explain the small associations found.

Third, comparison of an albuterol group with an albuterol plus inhaled corticosteroid group could be biased by severity or type of disease (asthma vs COPD). Most of our sample included patients with a diagnosis of asthma, and we controlled for this in our analyses. Patients with COPD were at higher risk for gastrointestinal events than patients with asthma, which could be related to the greater numbers of comorbidities and frequency of hospitalization in patients with COPD. Fourth, we chose not to match the index date of the albuterol cohort to the index date of the albuterol plus inhaled corticosteroid cohort because of the extent to which this would limit our sample size. However, this decision could have introduced a time bias that could have biased our HR upward.

Fifth, our end point was a diagnosis made by a physician using a variety of means including clinical acumen and diagnostic procedures such as endoscopy. Our study results would have been more compelling were we to use only endoscopic results. However, such procedural data were available on a limited number of patients who are not likely generalizable to our overall patient population prescribed inhaled pharmacotherapy for airways disease. Sixth, we did not adjust our analysis for use of antacids or gastroprotective drugs because of the sporadic use of these drugs, and primarily with the drugs available during the early years of observation (e.g., liquid antacids and histamine antagonists). Future studies should consider this important confounder.

Finally, our earlier archived data accurately and consistently reflect only prescription date and drug, but not dosage, which was the reasoning for using more recent data to explore dose effect. To some extent, our design accounted for the length of drug exposure by censoring observations at the time the drug no longer appeared in the records, but we were unable to

control for adherence. We are also limited in our understanding of the relationship among drug potency, device, and variability in administration technique—factors that could affect drug absorption in the gastrointestinal tract.[33, 35] Although our study did not include dry-powder delivery devices, market shift toward such formulations warrants further study of the effect of delivery device. Our indicator of spacer use was based on whether a patient received one, not whether the spacer was used properly or at all.

Conclusion

Patients prescribed inhaled corticosteroids may have a risk of adverse gastrointestinal events that is mitigated with the use of spacer devices. Although the frequency of such events is low (~6%), these results provide further support for the use of spacer devices with inhaled corticosteroids. Although we cannot determine whether patients using dry-powder devices are at increased risk for gastrointestinal events, our findings have potential implications for these newer devices since spacers cannot be used. Additional research should focus on dry-powder delivery devices to determine whether recommendations might be strengthened in this area.

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