Respiratory Medicine 131 (2017) 135–140

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

The impact of inappropriate use of short acting beta agonists in asthma

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ARTICLE INFO

Article history:
Received 29 April 2017
Received in revised form
10 August 2017
Accepted 14 August 2017
Available online 17 August 2017

Keywords:
Asthma
Reliever therapy
Short-acting beta-agonists
Outcomes
Costs

ABSTRACT

Background: Inappropriate use of short-acting beta-agonists (SABA) has been associated with increased morbidity and mortality in asthma. However, the extent and pattern of SABA use have changed significantly over recent years. The outcomes in patients who are contemporarily receiving inappropriate doses of SABA have not been evaluated.

Methods: We used population-based administrative health data from British Columbia (BC), Canada, to create a cohort of asthma patients aged 14 to 55. The exposure of interest was inappropriate use of SABA with any given 12-month period, as defined and validated previously. The primary outcome was asthma-related hospitalization in the following three-month period; secondary outcomes were asthma-related emergency department (ED) visits, asthma-related intensive care unit (ICU) admissions, and asthma-attributable costs.

Results: A total of 343,520 individuals contributed 2,127,592 patient-years of follow up. Of these, in 190,546 patient-years (7.7%) SABAs were used inappropriately. Inappropriate use of SABAs in any given year was associated with a 45% (odds ratio (OR) = 1.45, 95%CI 1.26–1.66) increase in the risk of asthma-related admissions in the following three-month period. Similarly, inappropriate use of SABA was associated with 25% (OR = 1.25, 95% CI 1.18–1.33) increase in the risk of asthma-related ED visits. The association with ICU admissions was not statistically significant. Inappropriate use of SABA was associated with a 6% (relative rate [RR] = 1.06, 95% CI = 1.04–1.08) increase in total-asthma-related costs.

Conclusions: Inappropriate use of SABA continues to be problematic in a significant minority of asthma patients and is associated with an increased health care utilization and risk of adverse outcomes.

1. Introduction

Asthma remains a global public health challenge with ongoing evidence of a significant number of subjects having uncontrolled disease [1]. Because asthma is highly prevalent and also commonly occurs in individuals in their most productive years, it exerts a significant economic and social burden [2,3]. Although for many years asthma guidelines have emphasized the importance of early introduction of asthma control therapy (medications with anti-inflammatory properties) most notably inhaled corticosteroids (ICS), many patients with asthma are reluctant to take these medications. The reasons for such non-adherence are multifactorial and include unfounded concerns regarding adverse events, lack of belief in the efficiency, or issues regarding affordability [4].

In contrast to controller therapies, rescue (reliever) medications such as short-acting beta agonists (SABA) should be reserved for occasional use to relieve symptoms [5]. Despite such recommendations, for many patients SABAs are the primary mode of treatment [6,7]. Historically, inappropriate and excessive use of SABA, and exposure to monotherapy with LABA, have been associated with worse outcomes and in the case of the excessive use of SABA

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http://dx.doi.org/10.1016/j.rmed.2017.08.014
0954-6111/

with an increased risk of death [6,8–12]. A recent review of asthma mortality in the UK showed a significant number of deaths were avoidable [13]. It has been shown that exposure to even low doses of anti-inflammatory therapy (namely ICS) eliminates the risk associated with the inappropriate use of both SABA and long acting beta agonists (LABA) [14]. But over-exposure to SABA and the absence of anti-inflammatory therapy continues to be prevalent [13].

There have been few recent population-based studies to assess the current pattern of use of SABA. To update this evidence gap, we have recently described the temporal trends and risk factors for the inappropriate and excessive use of SABA in a population-based study of asthma in British Columbia (BC), Canada [15]. Importantly, we have noted significant temporal trends in inappropriate and excessive use of SABA over time (e.g., annual reduction of 5.3% in inappropriate use of SABAs from 2002 to 2013) [15,16]. Such dynamic trends indicate that the characteristics of patients who are exposed to inappropriate doses of SABA might have significantly changed in recent years. As such, the associations between such exposure and adverse asthma-related outcomes might have also changed since the previous studies. The aim of the present work was therefore to update the evidence base on the consequences of inappropriate or excessive use of SABA using large, population-based data in a well-defined geographic area.

2. Methods

We used population-based administrative health data from BC, which is a Canadian province with a population of 4.7 M (as of 2015) [17]. Centralized databases have been established to administer the province's universal health-care system. We had access to birth and deaths [18,19], inpatient services use [20], outpatient services use [21], medication dispensation [22], as well as demographics and census databases [23] (the latter enables estimating socio-economic status (SES) based on neighborhood income quintiles). The Clinical Research Ethics Board at the University of British Columbia approved this study (H15-00062). All inferences, opinions, and conclusions drawn in this research are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

2.1. Asthma cohort

We used a validated case definition to create a cohort of diagnosed asthma patients [24–27]. In this case definition, a patient is considered as having asthma if during any rolling 12-month period they satisfy one of the following three criteria: one hospitalization with the main discharge diagnosis of asthma, two outpatient physician visits with the main diagnostic code for asthma, or three asthma-related medication dispensations (on different dates). We used ICD-9 code 493.xx and ICD-10 codes J45/J46 for identifying asthma-specific inpatient and outpatient records. A list of asthma-related medication was also used for interrogating the prescription records (list available in Appendix I).

Within this cohort, we applied a 'look-back' algorithm from the date the case definition was satisfied to find the first date each individual used any asthma-related resource. We refer to this date as the *index date* which marks the beginning of follow-up. Individuals between ages 14 and 55 at the index date were selected for the analysis. Follow-up period for the participants ended in the earliest of following: date of death, end of study period, or the last date of resource use of any type. Follow-up time was divided into adjacent one-year periods, with the potentially truncated last period excluded from the analysis. Fig. 1 provides details of the study design.

2.2. Exposure

The exposure of interest was inappropriate use of SABA, as defined in previous studies [28,29]. A patient-year was marked as inappropriate use if an individual used 2 or more puffs of SABA per week in the absence of any ICS or used more than 9 canisters of SABA during the year and no more than 100 μg/day of ICS [29]. As is typical with administrative databases, usage was inferred from the amount of filled prescriptions. Exposure was assessed independently for each patient-year starting from the index date.

2.3. Outcomes

The primary outcome was asthma-related hospitalization, defined as an episode of admission to hospital with the main diagnostic code for asthma (ICD-9 codes 493.xx, ICD-10 codes J45, J46). Secondary outcomes were asthma-related Emergency Department (ED) visits, asthma-related intensive care unit (ICU) admissions, and asthma-attributable costs. All outcomes were assessed in the three-month period after each exposure period to ensure the temporal separation of exposure and outcome windows to avoid time-dependent biases (outcomes affecting exposure) [30]. Asthma-related ED visits were identified based on the billing codes for ED-based physicians [31]. Asthma-related ICU admissions were identified as the subset of asthma-related hospitalizations with at least one day of ICU stay. Asthma-attributable costs were the sum of inpatient costs, outpatient costs, as well as costs of medications [32,33]. For inpatient costs, we multiplied each admission's Resource Intensity Weight (a variable in the data representing the intensity of admission in terms of resource use) with the average costs of hospitalization in the province in the corresponding fiscal year [34]. For outpatient services and medication dispensations, cost data were directly available in the respective datasets. Only inpatient and outpatient services with asthma as the primary discharge/diagnostic code were included. Attributing a medication dispensation record to asthma was based on *a priori*-compiled list of asthma-related medications (Supplementary Material).

2.4. Potential confounders

The analysis was adjusted for a relatively comprehensive set of confounding variables. Socio-demographic variables included sex, age at baseline, and socio-economic status (SES). We defined SES with income quintiles inferred from the geographic neighborhood. To control for the severity of asthma, we included the number of asthma-related hospitalizations, use of any systemic corticosteroids (either as intermittent which was defined as period of use lasting fewer than 14 days, or continuous which was defined as use during more than 50% of the year), and the extent of controller medication use during each exposure window. The latter was defined according to the method developed by Laforest et al. as the ratio of ICS (either in single-inhaler or combination-inhaler with long-acting beta-agonists) to all asthma-related medications and was dichotomized around the recommended cut-off point of 0.5 [35,36]. All these variables were determined for each patient-year (exposure window). We also controlled for comorbidity at baseline (first year of follow-up) measured through the modified Charlson comorbidity index (removing respiratory-related conditions) [37]. We further adjusted for indicators of the quality of care, namely the continuity of care (CoC) score [38], and whether pulmonary function test (PFT) was performed within each exposure window. For each patient-year, CoC was measured based on the Bice-Boxeman index and was presented as a value between 0 and 1 [38]. A score of zero means that all physician visits during the year by the patient had been to different physicians and a score of 1 means that all