Respiratory Medicine (2012) **106**, 1487–1493

Available online at www.sciencedirect.com

SciVerse ScienceDirect

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

Risk of new onset diabetes mellitus in patients with asthma or COPD taking inhaled corticosteroids

P.M. O'Byrne [a,*], S. Rennard [b], H. Gerstein [a], F. Radner [c], S. Peterson [c], B. Lindberg [c], L.-G. Carlsson [c], D.D. Sin [d]

[a] *Firestone Institute of Respiratory Health, Michael G DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada*
[b] *Internal Medicine Section of Pulmonary and Critical Care, Nebraska Medical Center, Omaha, USA*
[c] *AstraZeneca Research and Development, Lund, Sweden*
[d] *Department of Medicine, University of British Columbia, Vancouver, Canada*

Received 11 May 2012; accepted 25 July 2012
Available online 15 August 2012

KEYWORDS
Budesonide;
Hyperglycaemia;
Side-effects

Summary
Background: A recent case-controlled study reported an increased risk of diabetes mellitus in patients treated with inhaled corticosteroids for asthma or COPD, versus age-matched controls.
Objective: The purpose of the current study was to evaluate whether there was an increased risk of new onset diabetes mellitus or hyperglycaemia among patients with asthma or COPD treated with inhaled corticosteroids.
Methods: A retrospective analysis evaluated all double-blind, placebo-controlled, trials in patients ≥4 years of age involving budesonide or budesonide/formoterol in asthma (26 trials; budesonide: $n = 9067$; placebo: $n = 5926$), and in COPD (8 trials; budesonide: $n = 4616$; non-ICS: $n = 3643$). A secondary dataset evaluated all double-blind, controlled trials in asthma involving the use of inhaled corticosteroids (60 trials; budesonide: $n = 33{,}496$; fluticasone: $n = 2773$).
Results: In the primary asthma dataset, the occurrence of diabetes mellitus/hyperglycaemia adverse events (AEs) was 0.13% for budesonide and 0.13% for placebo (HR 0.98 [95% CI: 0.38–2.50], $p = 0.96$) and serious adverse events (SAEs) was 0% for budesonide and 0.05% for placebo. In the secondary dataset, the occurrence of diabetes/hyperglycaemia as AE and SAE was 0.19% and 0.03%, respectively. In the COPD dataset, the occurrence of diabetes mellitus/hyperglycaemia AEs was 1.3% for budesonide and 1.2% for non-ICS (HR 0.99 [95% CI: 0.67–1.46], $p = 0.96$) and SAEs was 0.1% for budesonide and 0.03% for non-ICS.

* Corresponding author. Rm 3W10, McMaster University Medical Center, 1280 Main Street West, Hamilton, Ontario L8S 4K1, Canada. Tel.: +1 905 521 2100; fax: +1 905 521 4972.
E-mail address: obyrnep@mcmaster.ca (P.M. O'Byrne).

0954-6111/$ - see front matter
http://dx.doi.org/10.1016/j.rmed.2012.07.011

Conclusion and clinical relevance: Treatment with inhaled corticosteroids in patients with asthma or COPD was not associated with increased risk of new onset diabetes mellitus or hyperglycaemia.

Introduction

Inhaled corticosteroids (ICS) are the mainstay of treatment for patients with asthma[1,2] and are an important part of the management of patients with chronic obstructive pulmonary disease (COPD), particularly those who have recurrent exacerbations.[3] While oral glucocorticosteroids may contribute in a dose-dependent manner to hyperglycaemia/impaired glucose tolerance and diabetes mellitus in vulnerable patients, the systemic concentrations achieved during ICS treatment for asthma or COPD are thought to be too low to affect plasma glucose in most patients. However, a large nested case-controlled study, involving patients treated with ICS for asthma or COPD, reported a 34% increase in the incidence of diabetes mellitus over 5.5 years of follow-up versus age-matched controls who were not treated with ICS.[4] By contrast, two other studies of ICS in elderly patients failed to demonstrate any increased risk of diabetes related to ICS exposure.[5,6] In a prospective cohort study of US veterans over 1 year, ICS exposure was associated with a dose-dependent increase in serum glucose concentrations in patients with established diabetes mellitus, but not in patients without diabetes.[7] Similarly, in a small, prospective, crossover study in patients with established type 2 diabetes mellitus, glycosylated haemoglobin levels rose significantly after 6 weeks of treatment with inhaled fluticasone.[8] Together, these observations suggest that ICS may exacerbate diabetes in asthma or COPD, by increasing blood glucose levels in patients with established diabetes mellitus. Their impact on incidence of diabetes mellitus, however, remains uncertain.

The ICS budesonide first became available in the early 1980s and is also available as a fixed-dose combination with the long-acting β_2-agonist formoterol for the treatment of asthma and COPD. The extensive clinical trial programme conducted for budesonide provides a considerable pool of patient data from which to examine the impact of ICS therapy on a variety of patient outcomes, including the risk for diabetes mellitus. The present pooled analysis was undertaken to determine whether ICS increases the risk of new onset diabetes mellitus or hyperglycaemia among patients with asthma or COPD treated with budesonide compared with those who did not receive budesonide in the randomised controlled trials.

Methods

Datasets

This study analysed data from all trials which used inhaled budesonide, and were randomized, double blinded, involved patients $\geq$4 years of age, who had either asthma or COPD, had a follow-up of more than 3 months (asthma) or $>$6 months (COPD) and were fully completed by December 2010.

Trials involving either placebo or active control therapies were included. This comprised 26 double-blind, placebo-controlled trials of budesonide or budesonide/formoterol in patients with asthma (included in the primary asthma dataset) (online repository Table), 34 double-blind active controlled trials of budesonide or budesonide/formoterol in patients with asthma (combined to give a total of 60 asthma trials in the secondary asthma dataset), and 8 double-blind trials of budesonide-containing products in patients with COPD, of which 7 were placebo-controlled (included in the COPD dataset) (online repository Table). Three trials with a duration of $>$1 year were censored at 365 days to allow cross-comparisons with other trials that were included in the analysis. Overall, the mean follow-up duration was 210 days in the 60 asthma trials and 268 days in the 8 COPD trials. The number of steroid naïve patients ranged from approximately 50% in the COPD trials, to between 0 and 100% in the asthma trials. Diabetes mellitus was not an exclusion criterion for any of these trials. The prevalence of diabetes was $<$1% in all of the asthma trials and between 5 and 10% in the COPD trials.

Outcome variables

Diabetes mellitus cases were identified as any adverse event (AE) or serious adverse event (SAE) coded to the MedDRA dictionary (version 13) as the term 'Diabetes mellitus (including subtypes)'; 'Diabetic ketoacidosis'; 'Diabetic hyperglycaemic coma' or 'Diabetic hyperosmolar coma'. Hyperglycaemia cases were identified as any AE (serious or non-serious) coded to the MedDRA dictionary (version 13) as the terms 'Hyperglycaemic conditions NEC', 'Blood glucose increased', 'Carbohydrate tolerance decreased', Glucose tolerance decreased, 'Glucose tolerance test abnormal' or 'Glycosylated haemoglobin increased'. Thus, diabetes AEs were defined as any new onset diabetes mellitus or worsening of existing diabetes. Patients with existing diabetes mellitus were not excluded, as the AEs were examined post randomization to either ICS or non-ICS treatment.

Statistical analysis

The risk of diabetes mellitus/hyperglycaemia as an AE or SAE was compared between patients assigned to budesonide or non-ICS treatments. Kaplan–Meier curves were generated to visually compare the time to the first reported cases of diabetes mellitus/hyperglycaemia AEs