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The risk and outcomes of pneumonia in patients on inhaled corticosteroids

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ABSTRACT

Corticosteroids are frequently prescribed anti-inflammatory medications. Inhaled corticosteroids (ICS) are indicated for Chronic Obstructive Pulmonary Disease (COPD) and asthma. ICS are associated with a decrease in exacerbations and improved quality of life in COPD, however multiple studies have linked the chronic use of ICSs with an increased risk of developing pneumonia, though the effect on mortality is unclear. We review the association of ICS with the risk of pneumonia and the implications on clinical outcomes.

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1. Introduction

Pneumonia is the leading cause of death related to infectious disease in developed countries and the eighth leading cause of death overall in the United States (US). In the US, pneumonia occurs in more than 5 million adults and accounts for more than 1 million admissions a year [1,2]. It is presumed that, in the US, pneumonia and influenza age-adjusted mortality is increasing [3].

Corticosteroids are anti-inflammatory medications commonly prescribed in respiratory medicine. Inhaled corticosteroids (ICS) are currently used for most patients with Chronic Obstructive Pulmonary Disease (COPD) and asthma [4,5]. The combination of ICS and Long Acting Beta Agonists (LABA) is considered a treatment of choice for patients with COPD with forced expiratory volume in the first second (FEV1) lower than 50% of predicted and two or more exacerbations per year [5,6]. Inhaled corticosteroids exert an anti-inflammatory and immunosuppressive effect that may affect the pathogenesis of pneumonia [7].

Several studies suggest that in COPD patients receiving chronic ICSs there is a higher risk of developing pneumonia [8–10]. However, the associated impact of ICSs on mortality and poor clinical outcomes among COPD patients who develop pneumonia is a matter of great controversy [11,12].

The purpose of this review is to assess the evidence related to the association of inhaled corticosteroids with the risk of community-acquired pneumonia (CAP) and other related clinical outcomes.

1.1. Methods

We reviewed published available manuscripts in PubMed by using the following search terms: “inhaled corticosteroids” and “pneumonia”. We limited the literature search to manuscripts published in the English language. The date of the most recent search was September 1, 2014.

2. Corticosteroids

Corticosteroids are involved in a wide range of physiological processes, including the regulation of inflammation, immune and stress responses, carbohydrate metabolism, protein catabolism, and serum electrolyte levels [13]. Corticosteroids can be administered through multiple routes, but for the purpose of this review we

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will focus on the corticosteroids that are administered through the inhalational route. Table 1 shows the most relevant ICS available on the market.

2.1. Mechanism of action

Corticosteroids inhibit the expression and action of many cytokines involved in the inflammatory response associated with pneumonia. At the cellular level, corticosteroids bind to a heterocomplex receptor located in the cytoplasm present in all human cells. This receptor is known as the glucocorticoid receptor (alpha-GR) [14], which is activated by corticosteroids, resulting in a drug–receptor complex that moves into the nucleus of the cell and binds this complex to the DNA. This will directly or indirectly regulate the transcription of target genes [15]. However, the anti-inflammatory and immunosuppressive effects of corticosteroids are due to three molecular mechanisms [7]. First, the ligand-activated alpha-GR binds as a homodimer to specific DNA sequences located in the promoter regions of target genes inducing transcription (transactivation). Second, an indirect negative regulation of gene expression (transrepression) is achieved by GR-protein interaction. The ligand activated receptor binds as a monomer to key pro-inflammatory transcription factors such as activator protein (AP)-1 and nuclear factor (NF)-κB. The resulting complex inhibits the initiation of transcription of relevant genes that play a central role in inflammation [7]. Corticosteroids inhibit the synthesis of several cytokines (e.g. tumor necrosis factor alfa [(TNF-alfa] and interleukins [IL] 4, 5, 6 and 13), adhesion molecules (e.g. ICAM-1, VCAM-1) and chemokines (e.g. eotaxin, IL-8) [15]. The third mechanism is corticosteroid signaling through membrane-associated receptors and second messengers (so-called non genomic pathways). The best-described non-genomic mechanism involves the activation of endothelial nitric oxide synthetase (eNOS), which is responsible for a rapid vasodilatory effect [16]. Other mechanism of action includes histone acetylation and deacetylation [17].

The mechanisms that could explain why ICSs may cause pneumonia are a matter of scientific interest. We hypothesized several possible explanations based on our review of the literature. The immunosuppressive effect caused by high local lung concentrations found with the use of ICSs may potentially increase the risk of pneumonia [18,19]. Barnes et al. [20] showed that in bronchial biopsies from patients receiving ICS/LABA (fluticasone propionate and salmeterol) the number of inflammatory cells was reduced and the expression of pro-inflammatory mediators was decreased. This suggests a possible decrease in local cellular defense mechanisms. This observation was confirmed in a multicenter randomized placebo-controlled trial, which also found a reduction of lung-specific inflammatory biomarkers [21]. The use of an ICS alone or in combination with LABA was associated with lower lung C-reactive protein (CRP), IL-6, and Surfactant protein D (SP-D) levels, but not systemic inflammatory biomarkers, except SP-D, when compared to placebo. Barbier et al. [22] demonstrated that fluticasone reduces bacterial airway epithelial invasion in a murine model of lung infection. And finally, as mentioned before it is possible that lipophilic ICS, such as fluticasone, may exert a stronger immunosuppressive effect, increasing mucosal and epithelial exposure facilitating pneumonic events.

Table 1
Types of inhaled corticosteroids.

Inhaled corticosteroids	Combination inhaled corticosteroids/ long-acting beta-agonists
	Beclometasone/Formoterol
Beclomethasone dipropionate	Fluticasone/Salmeterol
Budesonide	Budesonide/Formoterol
Flunisolide	Mometasone/Formoterol
Fluticasone propionate	Fluticasone/Vilanterol
Mometasone furoate	
Triamcinolone acetonide	
Ciclesonide	

3. Inhaled corticosteroids

Inhaled corticosteroids (ICS) are commonly prescribed medications for the management of patients with COPD and asthma [4,5,23]. In COPD, they are recommended for patients with severe obstruction (GOLD III or IV) and/or frequent exacerbations [5]. ICSs are recommended for patients with asthma and persistent symptoms [4,24].

The pharmacokinetics of the available inhaled corticosteroids has been described extensively [25,26]. Briefly, the use of ICSs, as opposed to systemic corticosteroids, improves the therapeutic index by decreasing systemic bioavailability, increasing systemic clearance, and prolonging residence time within the lung volume of distribution [27]. All available ICSs may produce systemic effects when administered in the high-dose range as defined by the guidelines [4,5].

Multiple studies have recognized an increased risk of pneumonia associated with the chronic use of ICS [8–10]. Pneumonia is associated with increased morbidity and mortality. In COPD, it is also associated with worsening quality of life and a decline in lung function [28]. Given their broad use, this has become a significant safety concern.

3.1. Inhaled corticosteroids and pneumonia

We reviewed the relevant literature assessing the association of ICSs and the risk of developing pneumonia among patients with COPD (Table 2). The Towards a Revolution in Chronic Obstructive Pulmonary Disease Health (TORCH) study [8], was the landmark randomized controlled trial (RCT) that suggested an associated increased risk of developing pneumonia among COPD patients treated with ICSs. The TORCH study compared the efficacy of salmeterol, fluticasone propionate, or a combination regimen (salmeterol/fluticasone 50/500 μg twice daily) against placebo in COPD patients over a 3-year period. COPD patients who received an ICS, as monotherapy or in combination therapy, had a higher rate of physician-reported pneumonia (19.6% and 18.3%, respectively) when compared to placebo (12.3%, $p < 0.001$). However, this study was limited by the lack of radiographic confirmation of the diagnosis of pneumonia. A post hoc analysis of the TORCH study reported by Crim et al. [29] confirmed these results, identifying advanced age, low body mass index, low FEV1, and the presence of an exacerbation in the previous year as risk factors for the development of pneumonia in COPD patients taking ICSs. After the publication of the TORCH trial, interest in assessing this association emerged around the world.

Kardos et al. [9], assessed the impact of combination therapy with salmeterol/fluticasone propionate 50/500 μg, twice daily, compared with LABA alone on the rates of moderate and severe acute exacerbations of COPD (AECOPD). The authors concluded that combination LABA/ICS therapy reduces the rate of moderate and severe AECOPD by 35% in patients with severe COPD ($p < 0.001$). However, the authors also found that pneumonia events were more likely to occur between COPD patients managed with LABA/ICS when compared to the LABA-only group (4.5 vs. 1.4%; $p = 0.005$). In addition, Wedzicha et al. [10], evaluated the effect of combination salmeterol/fluticasone propionate 50/500 μg twice daily vs. tiotropium on reducing exacerbations among patients with COPD. The authors conclude that pneumonia events were more common