Respiratory Medicine (2007) **101**, 1007–1014

ELSEVIER

respiratoryMEDICINE

The role of intrinsic efficacy in determining response to a β_2-agonist in acute severe asthma ☆

Nicola A. Hanania[a,*], Robert H. Moore[b], Janice L. Zimmerman[a], Charles T. Miller[c], Remzi Bag[a], Amir Sharafkhaneh[a], Burton F. Dickey[d]

[a]*Department of Medicine, Baylor College of Medicine, Houston, TX, USA*
[b]*Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA*
[c]*Departments of Cardiovascular Surgery and Biostatistics, University of Texas Health Sciences Center, Houston, TX, USA*
[d]*Department of Pulmonary Medicine, MD Anderson Cancer Center, Houston, TX, USA*

Received 21 April 2006; accepted 30 August 2006
Available online 17 October 2006

KEYWORDS
Acute asthma;
Beta-agonists;
Albuterol;
Isoproterenol;
Intrinsic efficacy;
Beta-adrenergic receptors

Summary
Background: Current guidelines recommend repeated doses of albuterol for the emergency treatment of acute asthma. However, approximately one-third of patients show little or no initial response to this partial β_2-agonist.
Methods: We conducted a randomized, double-blind, proof-of-concept study to investigate whether a *full* β_2-agonist, isoproterenol, offers a therapeutic advantage in adults presenting with acute severe asthma ($FEV_1 < 50\%$) who fail to respond to an initial treatment of the *partial* β_2-agonist, albuterol. Study subjects were randomized to receive a 2-h continuous nebulization of either albuterol (7.5 mg/h) ($n = 10$, mean $FEV_1 = 37\%$ predicted) or isoproterenol (7.5 mg/h) ($n = 9$, mean $FEV_1 = 33\%$ predicted). Respiratory symptoms, vital signs and pulmonary function measures were collected.
Results: Subjects from both treatment groups had similar baseline characteristics. The percent improvements from baseline FEV_1 at 60 and 120 min were significantly higher in subjects receiving isoproterenol than those receiving albuterol (44 vs. 17% and 63 vs. 24%, respectively, $P < 0.05$). The change in symptoms measured by the modified Borg score was also significantly greater in subjects receiving isoproterenol ($P < 0.01$). Both treatments were well tolerated, though the mean increase in pulse rate at 60 and 120 min (21 vs. 1 and 23 vs. 6 beats/min, respectively, $P < 0.05$) and the mean change in serum potassium at

☆ Presented as an abstract at the American College of Chest Physicians' meeting, Seattle, WA, October 2004.

*Corresponding author. Tel.: +1 713 8733454; fax: +1 713 8733346.
E-mail address: Hanania@bcm.tmc.edu (N.A. Hanania).

doi:10.1016/j.rmed.2006.08.023

120 min (−0.52 vs. −0.07 meq/L, $P<0.05$) from baseline were significantly greater in the isoproterenol group.
Conclusions: Our data suggest that in subjects presenting with acute severe asthma who fail to show an initial response to albuterol, the use of a β_2-agonist of higher intrinsic efficacy can be more effective in improving lung function and symptoms.

Introduction

Asthma is a common chronic inflammatory disease of the airways with significant morbidity and mortality.[1,2] Considerable progress has been made in understanding the pathogenesis of asthma and improving its treatment. Despite improvements in the outpatient care of asthma, the emergency treatment of acute asthma remains inadequate.[3,4] Among the 2 million patients presenting to US hospital emergency departments (ED) with acute exacerbations every year, approximately one-third fail to show sufficient improvement to allow safe discharge, and instead require admission to the hospital and sometimes to the intensive care unit.[1–6]

Prompt management of acute asthma is essential to prevent complications.[3,4] Managing patients with acute asthma involves assessing the severity of exacerbation, implementing measures to rapidly reverse airflow limitation, and instituting therapies such as systemic corticosteroids to limit the progression of airway inflammation.[7] β_2-Adrenergic agonists are the most powerful bronchodilators known, and their use is a mainstay of the initial treatment of acute exacerbation of asthma.[7] Despite more than a century of drug development and the current availability of numerous β_2-agonists of widely differing pharmacologic properties, the optimal use of these agents in the management of asthma is not fully determined.

β_2-agonists are generally classified by their receptor selectivity, duration of action, affinity, potency and intrinsic efficacy.[8–10] Intrinsic efficacy refers to the ability of a drug, independent of tissue conditions, to interact with a receptor to activate its downstream signal transduction pathway. It serves as a measure of the relative agonism of a drug or a hormone—i.e., a *partial* agonist is less effective than a *full* agonist in causing a downstream cellular response once bound to its receptor at equal receptor occupancy. The measurement of intrinsic efficacy has uncovered dramatic differences between drugs used clinically that had not been previously apparent in many studies of comparative efficacy. A simple formula to determine the intrinsic efficacy of a β_2-agonist based on measurements of affinity (dissociation constant, K_D) and potency (EC_{50}) has recently been reviewed.[10] The intrinsic efficacy of the most widely used β_2-agonist for the emergency treatment of acute asthma, albuterol, is only 5% that of epinephrine or isoproterenol, which are considered *full* β_2-agonists.[10–12]

Current asthma guidelines recommend repeated doses of albuterol, as needed, for the initial emergency treatment of acute asthma,[7] but do not recommend stepping up therapy to an agonist of higher intrinsic efficacy in patients who fail to adequately respond to albuterol. We hypothesized that the use of β_2-agonists of high intrinsic efficacy (full agonist) may lead to better outcomes in the emergency treatment of patients with acute severe asthma who fail to show an initial response to a partial agonist. To address this issue, we initiated a randomized, double-blind, proof-of-concept study to compare the full β_2-agonist, isoproterenol, with the partial β_2-agonist, albuterol, in acute severe asthma. The results of this study have previously been reported in part in the form of an abstract.[13]

Methods

Study subjects

Adults (18–50 years old) presenting with acute asthma to Ben Taub General Hospital's ED in Houston during the years 1998–2000, were screened for enrollment. Subjects were required to have a history of physician-diagnosed asthma for at least 6 months, be non-smokers or have past history of smoking <10 pack years, and have an $FEV_1<50\%$ of predicted after one initial therapy with nebulized albuterol (2.5 mg) administered in the ED on arrival. Subjects with significant comorbid conditions, those with other respiratory conditions, pregnant women, and those suffering from a life-threatening exacerbation such as those with impending respiratory failure (severe hypercapnia or hypoxemia), hemodynamic compromise, or those needing ICU admission, intubation or non-invasive ventilation were excluded. The study was approved by Baylor College of Medicine's Institutional Review Board, and all subjects gave written informed consent to participate.

Study design

This was a single center, double-blind, randomized parallel group study. Subjects who met the eligibility criteria were randomized in a double-blind fashion to receive either albuterol sulfate 0.083% solution (7.5 mg/h) (Dey Inc, Napa, CA) or isoproterenol 1:200 solution (7.5 mg/h, Sanofi Winthrop Pharmaceuticals, NY). Randomization was performed locally by the hospital's research pharmacy. The study medications were preservative free and were diluted in 20 mL of saline and administered over 2 h by continuous nebulization using an Airlife Misty Max 10™ nebulizer. All study subjects received prednisone 60 mg orally upon randomization and continuous oxygen 3 L/min by nasal cannula.

Efficacy measures

Serial peak flow meter (PEFR) measurements were performed using a Wright peak flow meter every 30 min, and