CHEST Original Research

ASTHMA

Population Pharmacodynamic Model of Bronchodilator Response to Inhaled Albuterol in Children and Adults With Asthma*

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Background: **Because interpatient variability in bronchodilation from inhaled albuterol is large and clinically important, we characterized the albuterol dose/response relationship by pharmacodynamic modeling and quantified variability.**

Methods: **Eighty-one patients with asthma (24% African American [AA]; 8 to 65 years old; baseline FEV_1, 40 to 80% of predicted) received 180 μg of albuterol from a metered-dose inhaler (MDI), and then 90 μg every 15 min until maximum improvement or 540 μg was administered; all then received 2.5 mg of nebulized albuterol. FEV_1 was measured 15 min after each dose. The population cumulative dose/response data were fitted with a sigmoid maximum effect of albuterol (Emax) [maximum percentage of predicted FEV_1 effect] model by nonlinear mixed-effects modeling. The influence of covariates on maximum percentage of predicted FEV_1 reached after albuterol administration (Rmax) and cumulative dose of albuterol required to bring about 50% of maximum effect of albuterol (ED_{50}) and differences between AA and white patients were explored.**

Results: **ED_{50} was 141 μg, and Emax was 24.0%. Coefficients of variation for ED_{50} and Emax were 40% and 56%, respectively. Ethnicity was a statistically significant covariate ($p < 0.05$). AA and white patients reached 82.4% and 91.9% of predicted FEV_1, respectively ($p = 0.0004$); and absolute improvement in percentage of predicted FEV_1 was 16.6% in AA patients vs 26.7% in white patients ($p < 0.0003$). There were no baseline characteristic differences between AA and white patients. Nebulized albuterol increased $FEV_1 \geq 200$ mL in 21% of participants. Heart rate and BP were unchanged from baseline after maximal albuterol doses.**

Conclusions: **Our model predicts that 180 μg of albuterol by MDI produces a 14.4% increase in percentage of predicted FEV_1 over baseline (11.7% in AA patients, and 17.5% in white patients). Emax varies widely between asthmatic patients. AA patients are less responsive to maximal doses of inhaled albuterol than white patients.** ***(CHEST 2008; 134:981–989)***

Key words: African American; albuterol; asthma; bronchodilator; cumulative dose of albuterol required to bring about 50% of maximum effect of albuterol; ethnicity; maximum effect of albuterol; metered-dose inhaler; nebulizer; pharmacodynamic model; white race

Abbreviations: ED_{50} = cumulative dose of albuterol required to bring about 50% of maximum effect of albuterol; Emax = maximum effect of albuterol; γ = Hill coefficient that describes the steepness of the dose/response relation; ICS = inhaled corticosteroids; MDI = metered-dose inhaler; PPK/PD = population pharmacokinetic/pharmacodynamic; R_0 = baseline percentage of predicted FEV_1; Rmax = maximum percentage of predicted FEV_1 reached after albuterol administration; SABA = short-acting β_2-agonist

Inhaled short-acting β_2-agonists (SABAs) are the most potent bronchodilators used today to treat acute symptoms of asthma[1]; and albuterol, a partial β_2-agonist, is the most frequently prescribed asthma medication in the United States.[2] Although universally used for acute asthma symptoms, SABAs have been associated with significant interpatient variability in response.[3–9] Many studies[3–12] have characterized the SABA dose to bronchodilator response relationship under controlled conditions. However, few studies have explored the magnitude and sources of bronchodilator response variability, and no studies

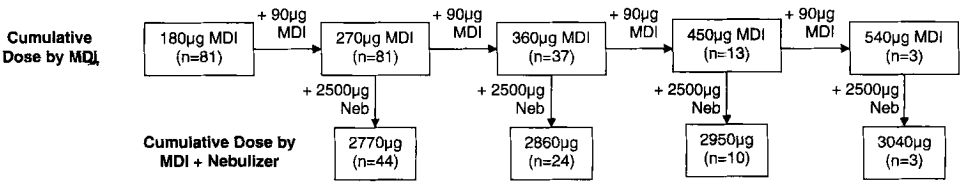

FIGURE 1. Number of participants who received each cumulative dose of albuterol. After baseline spirometry, participants received 180 μg of albuterol and then 90 μg every 15 min until maximum improvement or 540 μg was administered; all then received 2.5 mg of nebulized albuterol.

have characterized the dose to bronchodilator response relationship using population pharmacokinetic/pharmacodynamic (PPK/PD) modeling.

In a patient-care setting, the purpose of PPK/PD modeling is to gain a better understanding of the quantitative guidelines for dosage individualization and optimization. Additionally, PPK/PD modeling allows one to identify and quantify fixed and random sources of variability that characterize the dose (or concentration) vs response relationship in the target population to be treated with the drug.[13]

American Thoracic Society guidelines state that an increase in FEV_1 of 12 to 15% above baseline measured 15 min following inhalation of 100 to 400 μg of a SABA, such as albuterol, by metered-dose inhaler (MDI) "suggest a significant bronchodilatation."[14] Additionally, this measurement is a criterion used to diagnose asthma.[1] However, it is not clear if these dosing recommendations will achieve maximal bronchodilator response in patients.

In the present study, we characterized the albuterol dose to bronchodilator response relationship in 81 children and adults with moderate-to-severe persistent asthma using a population pharmacodynamic approach. The purpose was to obtain estimates of the pharmacodynamic parameters that characterize the albuterol dose/bronchodilator response curve, quantify and identify sources of interpatient pharmacodynamic variability, and determine the additional bronchodilator effect of a single dose of nebulized albuterol after maximal dosing from an MDI.

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MATERIALS AND METHODS

Participants

Participants of any ethnicity 8 to 65 years old with a well-defined history of physician-diagnosed asthma; a baseline pre-bronchodilator FEV_1 of 40% to 80% predicted for age, height, and gender[15,16]; who denied oral corticosteroid use, emergency department visits, or hospitalizations within the previous 3 months; who were nonsmokers or had < 5–pack-year history with no smoking in the previous year; and who had a normal physical examination and no confounding diseases were selected. Participants had to withhold inhaled SABAs or inhaled anticholinergic drugs for 8 h, oral antihistamines for 5 days, theophylline for 24 h, and cromolyn, nedocromil, and inhaled corticosteroids (ICS) for 2 h prior to the study. Inhaled salmeterol and formoterol and leukotriene modifiers were not available in the United States when this study was conducted. Participants were recruited from our asthma research clinic database or newspaper advertisements. The study was approved by our local Institutional Review Board, and written informed consent was obtained.

Study Design and Drug Administration

This was an open-label study conducted over 1 to 2 h for each participant on a single day. After we obtained baseline spirometry, heart rate, and BP measurements, participants received two inhalations of albuterol (90 μg per inhalation) from an MDI attached to a holding chamber (InspirEase; Schering-Plough Corporation; Kenilworth, NJ). Additional inhalations of 90 μg through the holding chamber were administered every 15 min, with spirometry, heart rate, and BP measured immediately prior to each dose. When there was no further improvement in FEV_1 (< 100 mL change from the highest FEV_1 obtained after the previous dose), each participant received a single 2.5-mg dose of nebulized albuterol. Final spirometry, heart rate, and BP measurements were obtained 15 min after nebulized albuterol. The cumulative doses of albuterol administered from the MDI were 180 μg, 270 μg, 360 μg, 450 μg, 540 μg; and the cumulative doses from the MDI plus nebulizer were 270 μg MDI plus 2,500 μg nebulized (2,770 μg); 360 μg MDI plus 2,500 μg nebulized (2,860 μg); 450 μg MDI plus 2,500 μg nebulized (2,950 μg); and 540 μg MDI plus 2,500 μg nebulized (3,040 μg). The number of participants receiving each dose and the cumulative administered doses (MDI and MDI plus nebulized) are shown in Figure 1. These doses represent the amount of drug administered to the patient from each device.

Prior to the first dose of study drug, two actuations from the albuterol MDI were discharged into the holding chamber to prime the MDI and to neutralize the electrostatic charge present in the plastic holding chamber.[17,18] The holding chamber was collapsed and expanded several times in a location away from the participant to remove any aerosolized albuterol from the interior