Effects of formoterol or salmeterol on impulse oscillometry in patients with persistent asthma

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Background: Effects of small-particle long-acting β-agonists on the small airways have been poorly documented.
Objective: We used impulse oscillometry (IOS) to compare single and repeated dosing effects of small- and large-particle long-acting β-agonists.
Methods: After a 1- to 2-week run-in period, patients received either 12 μg of small-particle hydrofluoroalkane 134a–formoterol solution or 50 μg of large-particle salmeterol dry powder twice daily plus inhaled corticosteroid for 1 to 2 weeks with a 1- to 2-week washout period in between. Measurements were made over 60 minutes after the first and last doses.
Results: Sixteen patients completed the study as follows: mean age, 43 years; FEV_1, 80%; forced midexpiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}), 48%; total airway resistance at 5 Hz, 177%; peripheral airway resistance as the difference between 5 and 20 Hz, 0.18 $kPa \cdot L^{-1} \cdot s$; Asthma Control Questionnaire score, 0.76; and inhaled corticosteroid dosage, 550 μg/d. There were significantly greater improvements with formoterol versus salmeterol in all IOS outcomes and FEF_{25-75}, but not FEV_1, at 5 minutes after the first dose, which were not sustained over 60 minutes. After the last dose, all IOS outcomes, but not FEV_1 or FEF_{25-75}, were significantly better with formoterol over the entire 60 minutes: mean difference at 60 minutes between formoterol and salmeterol in total airway resistance at 5 Hz, 7.50% (95% CI, 1.56% to 13.43%, $P = .02$); central airway resistance at 20 Hz, 5.37% (95% CI, 0.13% to 10.62%, $P = .045$); peripheral airway resistance as the difference between 5 and 20 Hz, 12.76% (95% CI, 1.28% to 24.24%, $P = .03$); reactance area under the curve, 19.46% (95% CI, 7.56% to 31.36%, $P = .003$); reactance at 5 Hz, 11.19% (95% CI, 4.62% to 17.76%, $P = .002$); and resonant frequency, 9.34% (95% CI, 3.21% to 15.47%, $P = .005$). Peak expiratory flow significantly improved to a similar degree with both drugs.
Conclusion: Significant improvements in IOS outcomes but not spirometry results occurred after chronic dosing with formoterol compared with salmeterol. This might reflect better deposition to the entire lung, including the small airways. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, small airways, spirometry, impulse oscillometry, long-acting β-agonist, formoterol, salmeterol*

Inhaled corticosteroid (ICS) with long-acting β-agonist (LABA) combination inhalers are now well established in current management guidelines as the preferred form of controller therapy in patients with persistent asthma. There is now increasing evidence to support a distinct asthma phenotype characterized by the presence of a disproportionate degree of persistent small-airways dysfunction.[1] It is possible to assess small-airways dysfunction in the so-called "silent zone" by using impulse oscillometry (IOS) to measure peripheral airway resistance as the difference between 5 and 20 Hz (R5-20) or peripheral airway capacitance as either the reactance area under the curve (AX) or reactance at 5 Hz (X5), as well as resonant frequency (RF).[2,3]

Spirometry can be used to derive volume-dependent airways closure as the forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}). IOS is an effort-independent test performed during normal tidal breathing to measure the frequency dependence of sound waves emanating from the bronchial tree and is considered more physiologic than spirometry, which tends to exaggerate small-airways closure associated with forced expiration.[1] Moreover, IOS is much easier and quicker to perform than spirometry, making it well suited to routine measurement in a busy clinic setting. Patients with the small-airways asthma phenotype who exhibit well-preserved FEV_1 in conjunction with abnormal R5-20 or FEF_{25-75} values, which in turn confers an increased risk of poorer long-term asthma control.[4] In a prospective study one IOS parameter (AX) showed sustained improvement over a prolonged period of follow-up in asthmatic children receiving controller therapy compared with spirometry.[5]

The advent of a small-particle hydrofluoroalkane 134a (HFA)–beclomethasone/formoterol combination solution metered-dose inhaler (Chiesi, Cheadle, United Kingdom) has provided the opportunity to target the entire lung in terms of both anti-inflammatory and smooth muscle responses in asthmatic patients associated with respective effects of ICS and LABA moieties. Although several clinical studies have attempted to differentiate between the effects of ICS formulations with different particle sizes,[6-11] relatively little attention has been given to the effects of LABA formulations on the small airways.[1]

The aim of the present proof-of-concept study was to assess the effect of particle size on bronchodilator response with IOS using 2 different LABAs currently licensed for add-on to ICSs in the United

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Abbreviations used
ACQ: Asthma Control Questionnaire
AX: Reactance area under the curve
FEF_{25-75}: Forced midexpiratory flow between 25% and 75% of forced vital capacity
FENO: Fraction of exhaled nitric oxide
HFA: Hydrofluoroalkane 134a
ICS: Inhaled corticosteroid
IOS: Impulse oscillometry
LABA: Long-acting β-agonist
PEF: Peak expiratory flow
R5: Total airway resistance at 5 Hz
R5-20: Peripheral airway resistance as the difference between 5 and 20 Hz
R20: Central airway resistance at 20 Hz
RF: Resonant frequency
X5: Reactance at 5 Hz

Kingdom, namely the 12-μg small-particle HFA-formoterol solution metered-dose inhaler (Chiesi) and 50-μg large-particle salmeterol dry powder inhaler (GlaxoSmithKline, Uxbridge, United Kingdom), which were chosen to represent 2 extremes of mass median aerodynamic diameter at 0.80 and 3.64 μm, respectively.[12,13] It is generally considered that particles less than 2 μm in diameter are able to optimally penetrate the small airways,[1] which is the reason for choosing the 2 formulations at different ends of the particle size spectrum. We elected to use what are normally considered therapeutically equivalent doses of formoterol (12-μg nominal ex valve dose = 10.1-μg delivered ex actuator dose) and salmeterol (50-μg nominal ex valve dose = 47-μg delivered dose).[14]

Specifically, we wanted to dissect out the independent effects of the different LABAs to obviate any potential confounding effect of different ICS moieties in their respective combination inhalers. Hence we decided to provide each LABA inhaler in addition to the same reference ICS therapy (as large-particle beclomethasone), with evaluation of airway responses after single and repeated dosing by using IOS and spirometry. Another reason for choosing the respective LABAs (rather than comparing small- and large-particle formoterol) is that the results from this study would presage a subsequent chronic dosing comparison of combination inhalers, namely 200/12 μg beclomethasone/formoterol solution (Chiesi) versus 500/50 μg fluticasone/salmeterol dry powder (GlaxoSmithKline).

METHODS

Study participants

Inclusion criteria were male or female volunteers aged at least 16 years with a diagnosis of persistent asthma, total airway resistance at 5 Hz (R5) of greater than 150% of predicted value, R5-R20 value of 0.05 $kPa \cdot L^{-1} \cdot s$ despite receiving ICS or ICS/LABA treatment, and FEV_1 of greater than 60%. Exclusion criteria were other significant respiratory diseases, an asthma exacerbation or respiratory tract infection requiring systemic steroids and/or antibiotics within 3 months of study commencement, and smoking within 1 year or a greater than 10 pack year history.

Study design

We carried out a single-center, randomized, open-label, crossover study (Fig 1). Patients were randomized to either 50 μg of dry powder inhaler salmeterol (GlaxoSmithKline) twice daily or 12 μg of HFA-formoterol solution (Chiesi) twice daily. The primary outcome was percentage change in R5-R20 from baseline. Secondary outcomes included percentage change from baseline in the remaining IOS variables (R5, central airway resistance at 20 Hz [R20], X5, RF, and AX), spirometry (FEV_1 and FEF_{25-75}), domiciliary peak expiratory flow (PEF), Asthma Control Questionnaire (ACQ) score, and fraction of exhaled nitric oxide (FENO).

At the screening visit, participants were converted to a reference HFA-beclomethasone dipropionate inhaler (Chiesi) with a mass median aerodynamic diameter of 2.9 μm[15] at an equivalent beclomethasone dipropionate dose, and any concomitant LABA was also stopped. After a 1- to 2-week run-in period, at visit 1, baseline measurements for IOS, spirometry, ACQ score, and FENO value were recorded. The first dose of the study inhaler was then administered in the department. IOS and spirometry were repeated at 5, 15, 30, 45, and 60 minutes after the first dose. After 1 to 2 weeks on the study inhaler, participants returned to the department for visit 2, with the penultimate dose of study inhaler being taken 12 hours before the study visit. Baseline measurements for the chronic dosing visit were recorded, and the last dose of the study inhaler was then administered. IOS and spirometry outcomes were recorded over 60 minutes as per after the first dose. Participants subsequently entered a wash-out period of 1 to 2 weeks, after which the same process was repeated with the other study inhaler after crossover at visits 3 and 4.

Measurements

IOS (Masterscreen IOS, Höchberg, Germany) was performed in triplicate, according to the manufacturer's guidelines. Spirometry was performed with a SuperSpiro (Micro Medical, Chatham, Kent, United Kingdom), and FENO values were measured with a NIOX analyzer (NIOX Nitric Oxide Monitoring System; Aerocrine AB, Solna, Sweden), according to American Thoracic Society guidelines.[16,17] Asthma control was assessed by using the 6-item ACQ.[18,19]

Ethics

The East of Scotland Research Ethics Service granted ethical approval (reference 13/ES/0050), and all patients provided written informed consent.

Statistical analyses

Sample size estimates were based on previous IOS data,[20] such that 16 patients would be required to complete per protocol to detect a 20% difference in the primary outcome of R5-20 achieving 80% power with an α error of .05 (2-tailed). We compared baselines according to treatment before the first and last doses of formoterol versus salmeterol. The respective baselines were then used to calculate the percentage changes for IOS and spirometry after single and chronic dosing. Repeated-measures ANOVA was applied to assess any treatment-time interaction over the 60-minute profile after single or repeated dosing. Hence the absence of a significant interaction indicates that any detectable differences between treatments are consistent over the 60 minutes, in turn resulting in a 95% CI for the overall treatment difference that excludes zero. Data for domiciliary peak flow were calculated as the average values from the last 3 days of the run-in, washout, and each repeated treatment period and were then compared by using paired Student *t* tests. SPSS version 21 (SPSS, Chicago, Ill) was used for all analyses.

RESULTS

Participant flow through the study is shown in Fig 2. Sixteen patients completed per protocol: mean age, 43 years; FEV_1, 80%; R5, 177%; R5-20, 0.18 $kPa \cdot L^{-1} \cdot s$; and ACQ score, 0.76 (Table I).

Baseline values before single or repeated dosing were not significantly different when comparing formoterol versus salmeterol (Table II). There were no differences when comparing baseline values between visits 1 and 3 after the run-in and washout periods, respectively.