METHODS. The experimental design involved a nonviable 8-stage Anderson Cascade Impactor (ACI) with a US Pharmacopeia (USP) throat model with a mean (SD) airflow rate of 28.3 (0.5) mL/min. Each of the 3 albuterol MDI products had their particle size assessed 6 times with and 6 times without spacer or holding chamber. With the use of high-performance liquid chromatography (HPLC) albuterol sulfate deposition was analyzed at each stage of the ACI.

RESULTS. Testing of MDI products without a VHC showed that Ventolin HFA had an inhalable dose of 21 μg and a noninhalable mean dose of 66 μg of albuterol sulfate, an inhalable fraction of 24%. In contrast, Proventil HFA had a mean inhalable dose of 40 μg and a noninhalable dose of 35 μg (58% inhalable fraction). ProAir HFA had a mean inhalable dose of 64 μg and a noninhalable dose of 42 μg, yielding a 61% inhalable fraction. All 3 of the products had inhalable doses significantly lower than their total doses. Nonetheless, there was only a significant difference ($P < .01$) between the mean total doses of Proventil HFA (75 μg) and ProAir HFA (107 μg). When a VHC was used, the inhalable fraction for Ventolin HFA was 94%, Proventil HFA 98%, and ProAir HFA 97%. However, the total dose for Ventolin HFA, Proventil HFA, and ProAir HFA were 25 μg, 54 μg, and 63 μg, respectively. These values were less in all 3 albuterol sulfate MDIs compared with when a VHC was not used. This indicates that larger, noninhalable particles were more likely to stick to the spacer device and are not deposited on the mouth or tongue, while the smaller inhalable particles were still delivered.

CONCLUSIONS. These results show a difference between the 3 products and their total dose delivered with or without spacer use. Ventolin HFA was found to deliver 2 to 3 times lower dose than Proventil HFA and ProAir HFA. The results in this study support that spacers increase the inhalable percentages of all 3 products while preventing deposition of larger, noninhalable particles on the mouth and tongue. This would likely decrease the side effect profiles on these medications.

REVIEWER COMMENTS. The ability to make well-informed decisions regarding safety and efficacy of the medications we prescribe for our patients is essential. All devices do not deliver the same amounts of medication. This study delivers more justification for recommending spacer use in our patients, as they may prevent the deposition of larger particles of the inhaled medications in the mouth and decrease the potential adverse side effect profile of these medications. Although these in vitro studies add evidence to previously published findings on differences between the various albuterol sulfate MDI products, in vivo studies are needed.

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Grace T. Padron, MD
Vivian P. Hernandez-Trujillo, MD
Miami, FL

Randomized Trial of Once-Daily Fluticasone Furoate in Children With Inadequately Controlled Asthma

Oliver AJ, Covar RA, Goldfrad CH, et al. *J Pediatr*. 2016;178:246–253.e2

PURPOSE OF THIS STUDY. To assess the efficacy, dose response, and safety of inhaled corticosteroid, fluticasone furoate (FF), in children with inadequately controlled asthma.

STUDY POPULATION. This was a multicenter, multicountry study with the following inclusion criteria: children between ages 5 to 11 years who had asthma symptoms at least 6 months before the study screening and who at the intake were on short-acting β-agonist (SABA) alone, SABA with leukotriene modifying agent, or SABA with low-dose inhaled corticosteroid for >4 weeks before the screening.

METHODS. The design is a phase IIb, multiple center, randomized, double-blind, placebo- and active-controlled study. The study assessed a 4-week pretreatment period, 12-week treatment period, and a 1-week follow-up period. The children were randomly placed in 1 of 5 groups including placebo, fluticasone propionate (FP) 100 mcg, FF at 25 mcg, 50 mcg, and 100 mcg. The primary endpoint was assessed by the mean change from baseline in daily morning peak expiratory flow (PEF) over the 12 weeks. Secondary endpoints such as rescue-free days were assessed to further expand on the clinical impact of the treatment. Pharmacokinetic and safety endpoints were also measured.

RESULTS. One thousand five-hundred forty children were initially assessed for eligibility for which 881 children were placed in the 4-week pretreatment period. Of those patients, 593 children entered the study and were randomly assigned to 1 of the 5 treatment groups. There was a statistically significant change from baseline daily morning PEF average over the 12 weeks in each FF dose group by an increase of 18.6 L/min (FF 25mcg), 19.5 L/min (FF 50 mcg), and 12.5 L/min (FF mcg 100); the P value was $< .001$ on all dose groups. The only significant PEF average increase above baseline in the FP group was for the 100 mcg (14.0 L/min with $P < .001$) dose. Importantly, there were statistically significant percent increases of rescue-free days in the FF 50 mcg and FF 100 mcg (9.8%, $P = .023$ and 12.2%, $P = .004$, respectively) which meant 0.7 and 0.9 rescue-free days per week. Adverse events (AEs) in FF treatment groups (32%–36%) were greater than in the placebo group (29%); the most frequent AE being cough.

CONCLUSIONS. The study suggested that both FP and FF had significant improvements compared with placebo in terms of asthma control. Although AEs were slightly increased over placebo, FP and FF were generally well-tolerated; therefore, both formulations are reasonable options for patients with uncontrolled asthma.

REVIEWER COMMENTS. FP is a common medication started for initial asthma maintenance therapy shown to improve patients' symptoms and PEF measurements. The study also suggests that a less commonly used medication, FF, has comparable efficacy with no new concerning adverse effects. This study shows there is a comparable alternative choice for providers to recommend on initiation of treatment as well as escalation of therapy for uncontrolled asthma.

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Jennifer Miller, MD
Lisa Forbes, MD
Houston, TX

Serious Asthma Events With Budesonide Plus Formoterol Vs. Budesonide Alone

Peters SP, Bleecker ER, Canonica GW, et al. *N Engl J Med*. 2016;375(9):850–860

PURPOSE OF THE STUDY. To evaluate whether the addition of formoterol to budesonide maintenance therapy increased the risk of serious asthma-related events in asthma patients.

STUDY POPULATION. The study included patients, 12 years and older, with persistent asthma who were receiving daily asthma medication and had 1 to 4 asthma exacerbations in the previous year. Patients with a history of life-threatening asthma were excluded. A total of 11 693 patients were enrolled at 534 centers, spanning 25 countries; 11 551 patients completed the study.

METHODS. In this double-blind study, patients were randomly assigned in a 1:1 ratio to receive either budesonide-formoterol or budesonide alone. Patients were stratified to a dose of inhaled glucocorticoid on the basis of initial assessment of asthma control and previous asthma therapy. Both treatment groups had similar demographic profiles and baseline characteristics, providing a broad representation of the overall asthma population. Adherence was assessed by utilizing a dose-actuation counter on the inhalers. During the treatment period, patients had 3 scheduled clinic visits (days 28, 84, and treatment end) and received monthly telephone calls. The primary end point of the study was the first serious asthma-related event, which was assessed as a time-to-event analysis. Serious events included adjudicated death, intubation, and hospitalization. The primary efficacy end point was the first asthma exacerbation, again assessed as a time-to-event analysis.

RESULTS. Serious asthma-related events occurred in 43 patients from the budesonide-formoterol group compared with 40 patients in the budesonide group (hazard ratio of 1.07; 95% confidence interval [CI] 0.70–1.65). There were 2 asthma-related deaths, both in the budesonide-formoterol group. Asthma exacerbation risk was 16.5% lower in the budesonide-formoterol group compared with budesonide alone (hazard ratio of 0.84; 95% CI 0.74–0.94; $P = .002$). The budesonide-formoterol group was shown to be statistically noninferior to budesonide alone for the time to first serious asthma-related event. Finally, analyses in prespecified subgroups defined by age, sex, race, and region were also consistent with the profile of the overall population studied.

CONCLUSIONS. In patients aged 12 and older with moderate-to-severe asthma, budesonide-formoterol combination therapy was associated with a lower risk of asthma exacerbations and a similar risk of serious asthma-related events compared with budesonide treatment alone.

REVIEWER COMMENTS. This randomized clinical trial showed that the addition of formoterol to budesonide did not appear to increase the risk of serious asthma-related events in patients with moderate-to-severe asthma. Furthermore, the risk of asthma exacerbation was significantly lower in patients taking budesonide-formoterol despite the high percentage of patients who reported asthma control at baseline. The AUSTRI trial, a US Food and Drug Administration–mandated study looking at safety of long-acting β adrenoceptor agonists (LABAs), was also recently published showing similar results of no evidence of an increased risk of serious asthma-related events with the addition of a LABA to inhaled corticosteroid monotherapy. One important limitation in this study to note is the exclusion of patients who have a history of life-threatening asthma. Although this exclusion was needed for patient safety, it is important to consider that these results may not be applicable in this patient population. Overall, these results are an important addition to the growing amount of evidence reviewing the risks and benefits associated with the use of LABAs in a fixed-dose combination with an inhaled corticosteroid.

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Todd Mahr, MD
Jennilee Eppley, PA-C
La Crosse, WI

Individualized Therapy for Persistent Asthma in Young Children

Fitzpatrick AM, Jackson DJ, Mauger DT, et al. *J Allergy Clin Immunol*. 2016;138(6):1608–1618.e12

PURPOSE OF THE STUDY. To determine if a differential response to asthma controller medications exists among young children with a history of wheezing requiring step 2 therapy and if this response can be predicted by phenotype and clinically available biomarkers.

STUDY POPULATION. Enrolled subjects were 300 children aged 12 to 59 months who required step 2 asthma therapy,

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