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Acute Effect of an Inhaled Glucocorticosteroid on Albuterol-induced Bronchodilation in Patients with Moderately Severe Asthma

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Key words: asthma, bronchodilation, albuterol, inhaled glucocorticosteroid, airway blood flow

Supported by an academic grant from Merck & Co, Inc

Conflicts of Interest: AW has received investigator-initiated academic grants from GSK, Forrest, Merck, Astra-Zeneca and serves on the Scientific Advisory Board of Aradigm. All other authors declare no conflicts of interest.

Abstract

RATIONALE: We have previously shown that in asthmatics a single dose of an inhaled glucocorticosteroid (ICS) acutely potentiates inhaled albuterol-induced airway vascular smooth muscle relaxation through a non-genomic action. An effect on airway smooth muscle was not seen, presumably because the patients had normal lung function. The purpose of the present study was to conduct a similar study in asthmatics with airflow obstruction to determine if an ICS could acutely also potentiate albuterol-induced airway smooth muscle relaxation in them.

METHODS: In 15 adult asthmatics (mean $\pm$ SE baseline FEV₁ 62 $\pm$ 3%), the response to inhaled albuterol (180 μ g) was assessed by determining the change in FEV₁(Δ FEV₁) for airway smooth muscle and in airway blood flow (Δ Qaw) for airway vascular smooth muscle measured 15 min after drug inhalation. Using a double-blind design, the patients inhaled a single dose of the ICS mometasone (400 μ g) or placebo simultaneously with or 30 min before albuterol inhalation.

RESULTS: After simultaneous drug administration, mean ΔFEV_1 was $0.20 \pm 0.05L$ (10%) after placebo and $0.32 \pm 0.04L$ (19%) after mometasone ($p < 0.05$); mean ΔQaw was -2% after placebo and 30% after mometasone ($p < 0.005$). When mometasone or placebo were administered 30 min before albuterol, there was a lesser and insignificant difference in ΔFEV_1 between the two treatments, while the difference in ΔQaw remained significant.

CONCLUSIONS: This pilot study showed that in adult asthmatics with airflow obstruction, a single standard dose of an ICS can acutely increase the FEV_1 response to a standard dose of inhaled albuterol administered simultaneously. The associated potentiation of albuterol-induced vasodilation in the airway was of greater magnitude and retained when the ICS was administered 30 min before albuterol. The clinical significance of this observation will have to be established by a study involving a larger patient cohort.

Introduction

Glucocorticosteroids inhibit the disposal of organic cations by blocking organic cation transporters expressed by non-neuronal cells through a pharmacologic non-genomic action, thereby interfering with the inactivation of the organic cations by intracellular enzymes (1-3). We have shown in human airway vascular smooth muscle cells that the glucocorticosteroid action on organic cation uptake occurs within minutes, does not involve gene transcription or protein synthesis, is not mediated through classical steroid receptors, and is cell membrane-linked (3,4).

This steroid effect is likely to acutely increase the concentration of organic cations including α - and β -adrenergic agonists at adrenergic receptor sites on smooth muscle. The airway contains two types of smooth muscle: airway smooth muscle and airway vascular smooth muscle. Therefore, inhaled glucocorticosteroids (ICS), owing to their inhibitory action on organic cation transporters, could be expected to decrease the local disposal of inhaled β_2 -adrenergic agonists and locally released nor-epinephrine, the latter resulting in vasoconstriction. Both ICS effects would potentiate inhaled β_2 -

adrenergic agonist-induced bronchodilation by interfering with the drug's local disposal and vascular clearance.

This non-genomic glucocorticosteroid effect has been confirmed in vivo by showing that high dose ICSs cause a dose-dependent decrease in airway blood flow that can be blocked with an α_1 -adrenergic antagonist (5,6), and by showing that the airway vascular smooth muscle response to inhaled albuterol is potentiated by pretreatment with a single low dose of an ICS that by itself does not cause vasoconstriction (7). An effect of the ICS on albuterol-induced bronchodilation was not seen, possibly because steroid-naïve mild asthmatics were included in the study; baseline airway caliber was in or near the normal range, presumably negating the possibility of detecting significant bronchodilation.

Thus, the previous study could not be satisfactorily interpreted with respect to its clinical relevance, i.e. acute potentiation of β_2 -adrenergic agonist-induced bronchodilation.

In the present proposal, we therefore wished to extend the previous study with a more informative protocol by administering a single standard dose of mometasone simultaneously with or 30 min before inhalation of a standard dose of albuterol in subjects with moderate persistent asthma who had airflow obstruction at the time of study. With this approach we wished to test the hypothesis that a single inhalation of an ICS causes an acute, dose-dependent potentiation of β_2 -adrenergic bronchodilation as assessed by spirometry. The associated airway vascular response was also determined by measuring airway blood flow.

Methods

Subjects

Never-smokers with physician-diagnosed asthma were considered for the study. They were allowed to use inhaled controller medication (including ICS) and rescue medication. At study entry, the subjects had to be clinically stable and to have a forced one-second expired volume (FEV₁) of < 75% of predicted (inclusion criterion). Exclusion criteria were the presence of cardiovascular disease and use of cardiovascular medications, pregnancy, use of oral controller medication for asthma

(methylxanthines, systemic glucocorticosteroids, leukotriene modifiers), and an acute respiratory infection within 4 weeks before enrollment. Fifteen subjects who met these criteria were enrolled in the study. The protocol was approved by the University of Miami Institutional Review Board (protocol #20071188) and registered with clinicaltrials.gov (NCT01210170). All subjects provided written informed consent.

Measurements

The forced expired volume in one second (FEV₁) served as an index of airway smooth muscle tone and Qaw as an index of airway vascular smooth muscle tone.

Spirometry: FEV₁ and forced vital capacity (FVC) were measured three times and the tracing with the highest FVC value was used for analysis. Predicted normal values for FEV₁ were taken from Crapo et al (8).

Airway blood flow (Qaw): This was measured with a non-invasive, previously validated soluble inert gas uptake method (9,10). The method determines the uptake of dimethyl ether (DME) from the anatomical deadspace during breathholds of different duration. From the decrease in expired DME concentration over time, DME uptake is obtained and from it Qaw is calculated using Fick's principle. Qaw is normalized for anatomical deadspace volume and expressed as $\mu\text{L} \cdot \text{min}^{-1} \cdot \text{mL}^{-1}$. Duplicate measurements were obtained; this required less than 5 minutes.

Systemic blood pressure, heart rate and arterial oxygen saturation by pulse-oximetry were monitored at each measurement point.

Protocol

Each subject made 5 morning visits to the research laboratory, separated by at least 5 days. The subjects were instructed to abstain from ingesting alcoholic beverages or using PDE₅ inhibitors for at least 12 hours before coming to the laboratory, and from having coffee or caffeinated drinks in the morning of the study day. Finally, the subjects

were asked to not use inhaled controller medication for at least 12 h and albuterol for at least 4 hours before coming to the laboratory.

Visit 1 (screening): On this visit, the subjects were informed about the study and signed an informed consent and the HIPAA form B. If they qualified for the study based on medical and medication history, they performed spirometry. Subjects whose FEV₁ as percent of predicted normal met the entry criterion were enrolled in the study. They were asked to return for 4 more visits (visits 2-5) for the following treatment protocols:

- Inhalation of 400 µg mometasone DPI 30 min before inhalation of 180 µg albuterol
- Inhalation of placebo 30 min before inhalation of 180 µg albuterol
- Simultaneous inhalation of 400 µg mometasone DPI and 180 µg albuterol
- Simultaneous inhalation of placebo and 180 µg albuterol

Using a double-blind design randomized for the order of treatment, the subjects inhaled, on different experiments days, 400 µg mometasone or placebo from identical DPI units provided by Merck & Co, Inc. Using a spacer, two puffs of HFA-albuterol (Ventolin®) delivered by a metered-dose-inhaler were administered 30 minutes or immediately after mometasone or placebo.

FEV₁ and Qaw along with systemic BP, heart rate and O₂ saturation were measured before mometasone or placebo inhalation, and before and 15 min after albuterol inhalation except on the day when mometasone and albuterol were co-administered; on that day the measurements were made before and 15 min after the mometasone/albuterol co-administration.

Statistical Analysis

Data were analyzed using JMP for Macintosh, version 4.0 (SAS Institute Inc., Cary, NC). Multi-factorial analysis of variance (ANOVA) was used to determine overall differences among treatments followed by a paired t test to identify specific pair differences and by the Tukey-Kramer test for differences among all pairs. Significance was accepted when $p < 0.05$.

Results

The patient characteristics are listed in table 1. All patients were long-term ICS users (2 subjects on 500 μ g fluticasone/50 μ g salmeterol twice a day, 5 subjects on 250 μ g fluticasone/50 μ g salmeterol twice a day, 7 subjects on 320 μ g budesonide/9 μ g formoterol twice a day). Their mean FEV₁ was 1.81 ± 0.12 L ($62 \pm 3\%$) on the screening day. On the two treatment days when placebo or mometasone were administered 30 min before albuterol, the mean pre-placebo and pre-mometasone FEV₁ and Qaw were similar to the corresponding pre-albuterol values. There were no differences in mean pre-albuterol FEV₁ and Qaw among the four treatment days (table 2). Similarly, there were no differences in mean systemic systolic and diastolic blood pressure, heart rate and O₂ saturation between the screening day values and the values obtained on the treatment days.

The immediate bronchodilator response to albuterol as assessed 15 min post drug administration was potentiated by the simultaneous administration of mometasone. In combination with placebo, albuterol increased mean FEV₁ by 0.2 liters (10%), while in combination with mometasone the response was significantly greater (0.32 L or 19%)($p < 0.05$) (table 3).

When mometasone or placebo was administered 30 min before albuterol, the albuterol-induced change in mean FEV₁ was 0.18 L (10%) after placebo and 0.27 L (16%) after mometasone (table 3, figure 1). The relative magnitude of the mometasone effect was less than after simultaneous drug administration, and the difference between mometasone and placebo was not statistically significant.

The vasodilator response to albuterol was quantitatively greater than the bronchodilator response, and significant whether mometasone was administered simultaneously with or 30 min before albuterol. With placebo, albuterol had no effect on mean Qaw ($-1.8 \mu\text{l}/\text{min}/\text{ml}$ or -2% and $0.2 \mu\text{l}/\text{min}/\text{ml}$ or 0%) (table 4, figure 2). The corresponding values for mometasone were $10.4 \mu\text{l}/\text{min}/\text{ml}$ or 30% and $7.7 \mu\text{l}/\text{min}/\text{m}$ or 18% ($p < 0.005$ for both).

Discussion

To our knowledge, this is the first study to show that a single administration on an ICS can acutely potentiate inhaled albuterol induced bronchodilation as assessed by spirometry in patients with moderate asthma. It has been previously reported that the acute bronchodilator response to formoterol was not enhanced by the co-administration of budesonide (11). That study included patients with acute asthma and the use of a long acting β_2 -adrenergic agonist, while our patients had moderately severe stable asthma and were treated with a short β_2 -adrenergic agonist. These differences may explain the discrepancy between the two studies.

An acute interaction between an ICS and a β_2 -adrenergic agonist has previously been shown for airway vascular smooth muscle responsiveness as reflected by Qaw but not for airway smooth muscle responsiveness as reflected by FEV_1 (7). Steroid-naïve mild asthmatics with essentially normal lung function were enrolled in that study, precluding the possibility of detecting significant changes in FEV_1 after albuterol administration. For that reason, we conducted the present study in patients with moderate asthma whose FEV_1 was below 70% of predicted.

Mometasone significantly potentiated the bronchodilator response to albuterol in these patients when the two drugs were administered simultaneously. The effect seems to wane by 30 minutes. When administered 30 minutes before albuterol, mometasone still enhanced the bronchodilator response to albuterol, but the magnitude of the effect was less and no longer statistically significant. This time course

is consistent with the proposed mechanism whereby glucocorticoids acutely potentiate β_2 -adrenergic responsiveness through a non-genomic inhibition of the β_2 -adrenergic agonist's disposal (1-4).

We chose recommended doses of mometasone and albuterol for the study. Therefore, the results can be considered clinically relevant in terms of the acute interaction between the two airway drugs and the magnitude of the enhanced FEV₁ response. Our patients were not steroid naïve. Indeed, all were regular ICS users and allowed to continue using the medication until 12 hours before coming to the laboratory. This indicates that long-term ICS treatment does not negate the acute effect of an ICS on albuterol responsiveness.

The present study confirmed our previous observation that the Qaw response to albuterol is blunted in patients with asthma, suggesting the presence of endothelial dysfunction (12, 13). The present study also showed that vascular reactivity can be restored with a single dose of an ICS as previously reported by us (7). Unlike in a previous study showing that long-term ICS can restore Qaw responsiveness to albuterol in steroid-naïve asthmatics (14), the ICS using asthmatics in the present investigation still had a blunted Qaw response to albuterol. Perhaps the difference can be explained by the fact that mild asthmatics were included in the previous studies while we recruited patients with moderately severe asthmatics with airflow obstruction in the present investigation. Patients with more severe asthma may be resistant to the vascular effects of long term ICS therapy.

It is not clear why the acute ICS effect on albuterol-induced relaxation is greater for airway vascular smooth muscle than airway smooth muscle. There is a greater expression of the steroid-sensitive organic cation transporter OCT3 in human airway vascular smooth muscle than airway smooth muscle, and the acute inhibition of the cellular uptake of hydrophilic β_2 -adrenergic agonists by steroids is also greater in airway vascular smooth muscle (15). While this could explain the differential non-genomic effect of mometasone on albuterol-induced vasodilation and bronchodilation in the present study, other mechanisms could also be involved.

We believe that the results obtained with mometasone in the present study reflect a class effect because previous studies involving different

ICS also showed a potentiation of albuterol-induced vasodilation in the airway (7- 16). However, a *in vitro* study has demonstrated potency differences among different glucocorticosteroids (17).

In a meta-analysis, Rodrigo (18) reviewed the rapid clinical effects of ICS in acutely exacerbated asthma. In this setting, ICS were found to have beneficial effects on peak flow, FEV₁ and hospital admissions in patients receiving standard care (including β_2 -adrenergic agonists). Although our study focused on the acute interaction between ICS and albuterol-responsiveness in patients with stable asthma, its results are consistent with the meta-analysis (18). In contrast to bronchodilation, the clinical significance of the acute ICS effect on albuterol-induced vasodilation is less clear. Possibly, the enhanced vasodilation could accelerate the local clearance of inflammatory spasmogens in the airway.

Our study addressed an exciting and novel interaction between ICSs and β_2 -adrenergic agonists. Thus far, this interaction has only been confirmed physiologically for airway vascular smooth muscle. The present study extended this concept to airway smooth muscle, a more important target in the treatment of asthma. The results of this pilot study will have to be supported by an investigation involving a larger number of patients with Δ FEV₁ as the primary outcome. Such a study combination of a short-acting β_2 -adrenergic agonist with an ICS could provide the basis for the development of new rescue formulations for patients with asthma.

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Acknowledgments

Author contributions: A. W. is guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article. A. W. contributed to conceiving the idea, patient management, and drafting and revising the manuscript for intellectual content; E. S. M. contributed to patient management, data analysis, and drafting the manuscript; L. C. and J.A. contributed to patient management and data collection.

Table 1. Patient Demographics

N	15
Mean age (range), yr	49 ± 3 (24-70)
Sex (M/F)	6/9
Heart rate (bpm)	71 ± 13
Systolic BP (mmHg)	117 ± 12
Diastolic BP (mmHg)	72 ± 8
SaO ₂ (mmHg)	96 ± 1
FEV ₁ (liters)	1.81 ± 0.12
FEV ₁ (%predicted)	62 ± 3

Table 2. Pre-albuterol FEV₁ and Qaw

Protocol	FEV ₁ (L)	FEV ₁ (% predicted)	Qaw (μ l/min/ml)
Simultaneous placebo-albuterol	1.96 $\pm$ 0.1	66 $\pm$ 4	42.1 $\pm$ 3.0
Simultaneous mometasone-albuterol	1.82 $\pm$ 0.16	62 $\pm$ 4	37.9 $\pm$ 1.6
Albuterol 30 min after placebo	1.81 $\pm$ 0.12	64 $\pm$ 5	45.9 $\pm$ 2.0
Albuterol 30 min after mometasone	1.82 $\pm$ 0.16	61 $\pm$ 4	48.8 $\pm$ 2.7

N=15. Mean $\pm$ SE. No significant differences among the 4 protocols.

Table 3. Effect of 400 μ g mometasone on albuterol-induced bronchodilation

	Δ FEV ₁	
	L	%
Simultaneous placebo-albuterol	0.20 $\pm$ 0.05	10 $\pm$ 2
Simultaneous mometasone-albuterol	0.32 $\pm$ 0.04*	19 $\pm$ 3
Albuterol 30 min after placebo	0.18 $\pm$ 0.04	10 $\pm$ 2
Albuterol 30 min after mometasone	0.27 $\pm$ 0.04	16 $\pm$ 3

Δ FEV₁: change in FEV₁ from immediately before to 15 min after 180 μ g albuterol. N=15. Mean $\pm$ SE. *p<0.05 vs. simultaneous placebo-albuterol

Table 4. Effect of 400 µg mometasone on albuterol-induced vasodilation in the airway

	ΔQ_{aw}	
	$\mu\text{l}/\text{min}/\text{ml}$	%
Simultaneous placebo-albuterol	-1.8 ± 1.5	-2 ± 3
Simultaneous mometasone-albuterol	$10.4 \pm 2.1^*$	30 ± 7
Albuterol 30 min after placebo	0.2 ± 2.3	0 ± 3
Albuterol 30 min after mometasone	$7.7 \pm 1.2^*$	18 ± 3

ΔQ_{aw} : change in Q_{aw} from immediately before to 15 min after 180 µg albuterol. N=15. Mean±SE. *p<0.005 vs. corresponding placebo-albuterol



