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Acute Effect of an Inhaled Glucocorticosteroid on Albuterol-Induced Bronchodilation in Patients With Moderately Severe Asthma

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BACKGROUND: We have previously shown that in patients with asthma a single dose of an inhaled glucocorticosteroid (ICS) acutely potentiates inhaled albuterol-induced airway vascular smooth muscle relaxation through a nongenomic 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 patients with asthma with airflow obstruction to determine if an ICS could acutely also potentiate albuterol-induced airway smooth muscle relaxation in them.

METHODS: In 15 adult patients with asthma (mean ± SE baseline FEV_1, 62% ± 3%), the response to inhaled albuterol (180 μg) was assessed by determining the change in FEV_1 (ΔFEV_1) for airway smooth muscle and in airway blood flow (ΔQaw) 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 μg) or placebo simultaneously with or 30 min before albuterol inhalation.

RESULTS: After simultaneous drug administration, mean ΔFEV_1 was 0.20 ± 0.05 L (10%) after placebo and 0.32 ± 0.04 L (19%) after mometasone ($P < .05$); mean ΔQaw was −2% after placebo and 30% after mometasone ($P < .005$). When mometasone or placebo was administered 30 min before albuterol, there was a lesser and insignificant difference in ΔFEV_1 between the two treatments, whereas the difference in ΔQaw remained significant.

CONCLUSIONS: This pilot study showed that in adult patients with asthma 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.

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ABBREVIATIONS: DME = dimethyl ether; DPI = dry powder inhaler; ICS = inhaled glucocorticosteroid; Qaw = airway blood flow

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Glucocorticosteroids inhibit the disposal of organic cations by blocking organic cation transporters expressed by nonneuronal cells through a pharmacologic nongenomic 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 classic 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 (ICSs), 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 norepinephrine, 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 nongenomic glucocorticosteroid effect has been confirmed in vivo by showing that high-dose ICSs cause a dose-dependent decrease in airway blood flow (Qaw) 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-naive patients with mild asthma 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 (ie, 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 Qaw.

Materials and Methods

Subjects

Never smokers with physician-diagnosed asthma were considered for the study. They were allowed to use inhaled controller medication (including ICSs) and rescue medication. At study entry, the subjects had to be clinically stable and to have an FEV_1 of $<75\%$ 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 Human Subject Research Office at University of Miami (protocol #20071188) and registered with clinicaltrials.gov (NCT01210170). All subjects provided written informed consent.

Measurements

The FEV_1 served as an index of airway smooth muscle tone and Qaw as an index of airway vascular smooth muscle tone. FEV_1 and FVC were measured by spirometry three times, and the tracing with the highest FVC value was used for analysis. Predicted normal values for FEV_1 were taken from Crapo et al.[8]

Qaw was measured with a noninvasive, previously validated soluble inert gas uptake method.[9,10] The method determines the uptake of dimethyl ether (DME) from the anatomic dead space during breath holds 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 anatomic dead space volume and expressed as μL/min/mL. Duplicate measurements were obtained; this required <5 min. Systemic BP, heart rate, and arterial oxygen saturation by pulse oximetry were monitored at each measurement point.

Protocol

Each subject made five morning visits to the research laboratory, separated by at least 5 days. The subjects were instructed to abstain from ingesting alcoholic beverages or using PDE_5 inhibitors for at least 12 h 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 h before coming to the laboratory.

On visit 1 (screening), the subjects were informed about the study and signed an informed consent and the Health Insurance Portability and Accountability Act form B. If they qualified for the study based on medical and medication history, they performed spirometry. Subjects whose FEV_1 as percent of predicted normal met the entry criterion were enrolled in the study. They were asked to return for four more visits (visits 2-5) for the following treatment protocols:

- Inhalation of 400 μg mometasone dry powder inhaler (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 experiment days, 400 μg mometasone or