INHALED CORTICOSTEROIDS AND THE BENEFICIAL EFFECT OF DEEP INSPIRATION IN ASTHMA

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METHODS

Description of single dose methacholine bronchoprovocations and calculation of % bronchodilation and bronchoprotection by deep inspirations

The modified, single dose methacholine bronchoprovocation was performed as follows: first, lung function measurements were obtained at baseline by a spirometric maneuver that combines a partial forced expiration (starting from end tidal volume) to residual volume, immediately followed by a deep inspiration to total lung capacity and by another forced expiration to residual volume. The inspiratory vital capacity (the volume of air inhaled from the residual volume that was attained by the partial forced expiratory maneuver to total lung capacity, IVC) and FEV_1 were recorded. In no instance was the residual volume calculated; however, the partial and maximal forced expiratory maneuvers were continued until a plateau in volume was obtained. The best of three acceptable and reproducible (within 5%) maneuvers was retained for analysis. After these baseline combination (partial/maximal) maneuvers, subjects were instructed not to take any deep breaths for a period of 20 minutes. At the end of this period, a single dose of methacholine was administered as five tidal inhalations. The starting concentration of methacholine was 0.075 mg/ml. After three minutes, still in the absence of deep breaths, a single combination spirometric maneuver was performed. The change from baseline in the post-methacholine FEV_1 was calculated. If the reduction in FEV_1 from baseline was less than 20%, the subject was invited to repeat this procedure on a separate occasion, at least 24 hours later, with an increased single dose of methacholine (approximately half log increment). This process was continued with additional visits and single dose

methacholine challenges until the single provocative dose causing 20% or more reduction in FEV_1 from baseline was determined. The maximum concentration of methacholine used in these single dose challenges was 75 mg/ml.

In the challenge where FEV_1 was reduced by 20% or more from baseline, the protocol was extended by inviting the subject to perform four deep inspirations, within a minute from the post-methacholine combination maneuver. Immediately following these deep inspirations, a combination spirometric maneuver was repeated. Each deep inspiration was performed slowly, without breath holding at total lung capacity, and was followed by passive exhalation to functional residual capacity. For the measurement of deep inspiration-induced bronchodilation, the changes from baseline in IVC and in FEV_1 at the end of the protocol (post deep inspirations) were compared to those obtained immediately after the methacholine administration (pre-deep inspirations). The % bronchodilation by deep inspiration was calculated as the difference in the % reduction in lung function from baseline between the pre- and post-deep inspiration maneuvers, divided by the % reduction in lung function from baseline obtained immediately after the methacholine administration (pre-deep inspiration).

% bronchodilation = (% reduction in IVC from baseline pre-deep inspirations) – (% reduction in IVC from baseline post-deep inspirations) / (% reduction in IVC from baseline pre-deep inspirations) x 100

To measure bronchoprotection by deep inspiration, subjects were asked to undergo, on yet another visit, an additional single dose methacholine bronchoprovocation utilizing the same concentration of methacholine as in the challenge that resulted in at least 20% reduction in FEV_1. During this procedure, after the 20-minute deep breath prohibition period and *immediately prior* to the inhalation of methacholine, subjects were instructed to take 5 consecutive deep inspirations to total lung capacity, as described for the bronchodilation protocol. Three minutes after the inhalation of methacholine, a combination spirometric maneuver was performed, as described above. For the measurement of deep inspiration-induced bronchoprotection, the changes from baseline in IVC and in FEV_1 at the end of this protocol, were compared to the respective changes in the protocol where no deep inspirations prior to the single dose methacholine challenge were taken. The % bronchoprotection by deep inspiration was calculated as the ratio of the difference in the % reduction in lung function from baseline between the above two protocols, divided by the % reduction in lung function from baseline obtained in the protocol that was devoid of pre-methacholine deep inspiration maneuvers.

% bronchoprotection = (% reduction in IVC from baseline in the absence of deep inspirations) – (% reduction in IVC from baseline with 5 deep inspirations prior to methacholine) / (% reduction in IVC from baseline in the absence of deep inspirations) x 100

Methacholine was delivered through a De Vilbiss 646 nebulizer (De Vilbiss Co. Somerset, PA), attached to a Rosenthal dosimeter (Laboratory for Applied Immunology, Inc, Fairfax, VA). The dosimeter was activated by the beginning of each inhalation (dose delay: 0.03 s; dose duration: 0.6 s) and was driven by compressed air at 30 psi. Spirometric measurements were performed using a computerized rolling seal spirometer (Warren E. Collins Inc. USA).