SHORT REPORT

Safety of inhaled corticosteroids delivered by plastic and metal spacers

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Background: Because of its non-electrostatic properties the metal Nebuchamber (NC) valved holding chamber (VHC) delivers a greater mass of aerosol to the mouth than the polypropylene Aerochamber (AC) VHC. Delivery of more aerosol to the lungs may also increase systemic absorption of inhaled corticosteroids (ICS) and hypothalamo-pituitary-adrenal (HPA) suppression.
Methods: Thirty children (mean 4.3 (SD 0.3) years) received 200 µg budesonide twice daily by NC or AC, both with the mask provided, in a randomised, two month crossover trial. Twenty four hour urinary free cortisol (UFC) was determined as a measure of HPA suppression.
Results: UFC decreased from 42.3 (7.8) nmol UFC/nmol creatinine control to 26.2 (2.4) (p = 0.06 *v* control) after AC, and to 24.5 (2.5) (p = 0.04 *v* control) after NC (p = 0.4 AC *v* NC).
Conclusions: Despite a greater total dose delivered to the mouth, NC is not associated with greater HPA suppression when using 400 µg/day budesonide under real life conditions in young children.

Inhaled corticosteroids (ICS) are an important part of asthma management, even in mild asthma.[1] The Nebuchamber (NC; AstraZeneca, Lund, Sweden) is a stainless steel valved holding chamber (VHC) with a mask. The steel body prevents accumulation of electrostatic charge. It has been shown in vitro that it delivers substantially more total aerosol mass than the charged, commonly used, plastic spacers.[2–4] If more aerosol is delivered, it is possible that the systemic absorption of the medication is increased. This could have major safety implications in children treated with ICS. Although the long term risk of "usual average dose" administration of ICS in school age children has been recently shown to be minimal,[5] there is hardly any safety data in preschool children. The purpose of the present study was to compare the short term systemic effects as reflected in 24 hour urinary free cortisol (UFC) excretion following delivery of inhaled corticosteroids by a metal (NC) or plastic (AeroChamber, AC; Trudell Medical International, London, ON, Canada) VHC.

METHODS

This was a randomised controlled, crossover, open study in the setting of outpatient paediatric primary care clinics (Israel Pediatric Research in Office Network).

Children with asthma, aged 2–6 years, who fulfilled the following criteria were included:

(1) Symptoms of asthma present at least once a week during the previous two months

(2) No oral or topical ICS use within one month preceding enrolment

(3) Demonstrated competence in the use of NC and AC

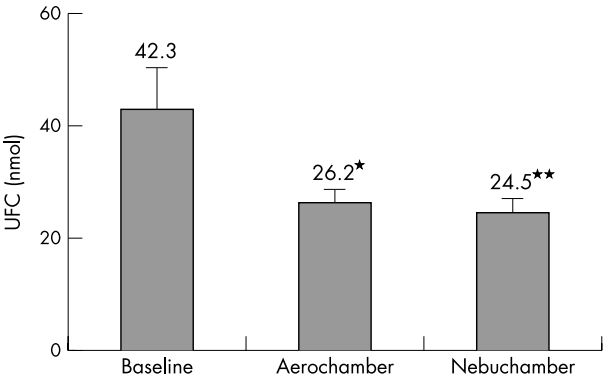

Figure 1 Urinary free cortisol (corrected for creatinine secretion) at baseline and after each treatment period (mean (SD)). *p = 0.06 *v* baseline; **p = 0.04 *v* baseline.

(4) Continent of urine day and night.

Following a 10–14 day run-in period, patients were randomly assigned to enter two consecutive four-week treatment periods. In each of these periods they received their prescribed ICS (400 µg/day budesonide) by means of a metered dose inhaler (MDI) attached to either the NC or AC.

Patients were instructed to wash their spacer according to the manufacturer's instructions.

The primary outcome was the excretion of free cortisol in 24 hour urine samples collected during the last weekend of each period. The first samples were collected at the end of the run-in period. Cortisol concentrations were measured using a commercial radioimmunoassay kit (DPC, Diagnostic Products Corporation, Los Angeles, CA, USA) with extraction. Urinary creatinine was determined to ensure the accuracy of the urine collection. The laboratory was blind to the experimental assignment of the samples.

Statistics

All data were analysed with the SPSS X2 statistical software. In order to test for interaction and group order influence, data were compared between the study groups (Nebuchamber first or Aerochmaber first) using ANOVA with repeated measurements for between and within subjects. Statistical tests were two sided, conducted at the 0.05 level. Paired *t* tests were used to compare UFC concentrations between the two treatments.

Based on previous UFC measurements in asthmatic children on similar ICS dosage,[6] we estimated that there would be a more than 90% chance of detecting a 25% clinically

Abbreviations: AC, Aerochamber; HPA, hypothalamo-pituitary-adrenal; ICS, inhaled corticosteroids; MDI, metered dose inhaler; NC, Nebuchamber; UFC, urinary free cortisol; VHC, valved holding chamber

meaningful difference between the treatment periods ($\alpha = 0.05$) when sample size (n) is 30 patients for each treatment group.

RESULTS

Thirty five patients were enrolled. Five defaulted during the first treatment period, of which three were on AC (one withdrew after a severe exacerbation and two failed to adhere to the protocol) and two were on NC (both failed to adhere). Mean age of the remaining 30 patients who completed the study was 4.3 (SD 0.3) years.

UFC (fig 1) decreased from 42.3 (7.8) (control) to 26.2 (2.4) nmol UFC/nmol creatinine ($p = 0.06$ *v* control) after AC, and to 24.5 (2.5) nmol UFC/nmol creatinine ($p = 0.04$ *v* control) after NC ($p = 0.4$ AC *v* NC).

DISCUSSION

All of the previous dosage recommendations for ICS by MDI and VHCs in children with regard to safety issues have been based on studies with plastic devices in school aged children. It has been assumed that no significant risks arise with doses up to 400 μg of daily budesonide. Increasing use of ICS in younger children with asthma justifies concern regarding safety with these dosages. Due to its non-electrostatic properties the Nebuchamber has been shown to deliver, in vitro, a substantially greater total dose of aerosol to the mouth compared to plastic VHCs. Thus, for the same nominal emitted MDI dose, it might be assumed that using NC, more ICS would be delivered to children, which raises the possibility not only of increased efficacy, but also concerns about safety.

To our knowledge, this is the first clinical study of the safety of the metal NC in preschool children. The results showed that under "real life" conditions, when young children used either the NC or AC, the degree of adrenal supression was similar. Our study highlights the discrepancy between in vitro evaluation using filters at the mouth and in vivo dose, distribution, and predicted efficacy of inhaled medication.[7] In vitro studies (measuring the dose delivered to a filter) are either performed with breathing simulators or with patients under strictly controlled conditions. Of note is that even with patients, the in vitro studies were mostly performed in the laboratory or in the clinic under the supervision of a study nurse or physician. Caregivers were often encouraged to hold the mask firmly against their child's face to ensure a tight seal and breathing patterns were coached. Unfortunately this is far from the situation in the real world where many young children often do not achieve a good seal between the mask and the face either due to poor compliance on the part of caregivers, lack of cooperation from the children, or poor mask design.[8]

Another likely explanation for our results is that priming a plastic VHC by repeated aerosol actuations greatly reduces the electrostatic charge on the walls.[9] This should happen within a few days of commencing the study and is likely to eliminate most of the electrostatic charge related difference in performance of these VHCs. As we did not measure the charges on the two spacers, this possibility cannot be confirmed. We are also well aware that the predictive value of short term studies for long term effects of ICS is poor. However, the principal aim of the present study was not to predict long term safety but to compare the safety profile of the metal NC VHC to that of the well established, universally used plastic AC VHC.

Further safety studies in this relatively large group of preschool children on chronic ICS therapy using MDI via VHC and face mask are needed.

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