495. Treating childhood asthma

P4815

Transparency in evidence-based pediatric asthma guidelines: GRADE and the other considerations

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Introduction: International evidence-based pediatric asthma guidelines are often not used in clinical practice. In step 3 of pediatric asthma management some guidelines make clear choices for LABA were others give alternative options, but without being transparent in why choices are made. To enhance the usefulness of guidelines, the ATS has chosen GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) as the preferred methodology for rating the quality of evidence and strength of recommendations in clinical practice guidelines.
Objective: Our aim was to develop transparent recommendations on step 3 of asthma management in children.
Methods: We used GRADE to assess the quality of evidence and separately reported other considerations. Final recommendations were formulated on both evidence as well as the other considerations in cooperation with the Dutch Society of Pediatric Pulmonologists.
Results: We found 7 RCTs comparing doubling the dose of ICS versus a combination of ICS and LABA and/or versus LTRA in children with symptomatic asthma despite normal ICS dose. According to GRADE, the quality of evidence was "moderate", both treatments were effective and individual response could not be predicted. Other considerations included safety, convenience and costs. We suggest in children with symptomatic asthma despite ICS, to first double the dose of ICS. If not effective, a combination of ICS and LABA can be prescribed. In case of adverse effects or poor inhalation technique a LTRA can be prescribed.
Conclusion: By using the GRADE approach together with other considerations clear recommendations for step 3 in asthma management were made. This approach might improve implementation.

P4816

A systematic review of underlying reasons for barriers to asthma management in ethnic minority children

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Background: Barriers to asthma management are an often cited explanation for poorer outcomes suffered by children from ethnic minorities. Empirical data explaining why and how barriers arise seem poorly articulated.
Methods: Systematic database and internet resources were searched for studies with a primary focus on barriers and facilitators in asthma in ethnic minority children aged 0-18 years. 47 eligible papers were identified, reviewed and data extracted by 2 independent reviewers. A systematic thematic narrative analysis was undertaken.
Results: Minority ethnic groups appear to share common barriers to asthma management. However underlying explanations differ between groups The analysis produced 6 categories of barriers: Knowledge and attitudes, treatment strategies, external influences, intrinsic factors, physician related factors and service related issues. Important gaps and methodological limitations in the literature were also identified including: variations in data quality; inadequate or absent considerations of the concept of ethnicity; variable definitions of asthma; reliance on closed-ended questionnaires which limit the breadth and depth of exploration of underlying explanations.
Conclusion: Further exploration of underlying explanations using open-ended qualitative techniques are required to elucidate ethnic variations in the mechanisms by which barriers to asthma management occur. When developing intervention strategies, practitioners and researchers should recognise that apparently similar barriers may have different explanation in different ethnic groups and tailor strategies accordingly.
Funding: This project is funded by Asthma UK. Study ID 10/037.

P4817

Low agreement between current and long-term asthma control in children: The PACMAN cohort study

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Background: Asthma control can be defined in various ways.
Objectives: To investigate the association between current and long-term asthma control.
Methods: We included 418 children using ICS participating in the PACMAN-cohort study. Current asthma control (last week) was defined using the ACQ. Long-term asthma control (last year) was based on GINA guidelines. This was analysed for the four different seasons separately. Not well-controlled asthma was defined as: ≥3 of the following items present in a specific season: day-time or night-time symptoms, limitations in activities and rescue medication use. Secondly, this first definition was adjusted for the frequency of symptoms during a season. When asthma control was present in ≥3 seasons we qualified this as long-term asthma control (control during the past year). Current and long-term asthma control were compared to investigate agreement.
Results: Long-term uncontrolled asthma rates were highest in winter (51%) and lowest in summer (33%) ($P < 0.05$). 42% of the patients did not have long-term asthma control during the past year. Overall agreement between current and long-term asthma control was 67% and kappa statistics (≤ 0.39) indicated "poor agreement".
Conclusion: The congruence between current and long-term asthma control is poor in our cohort of asthma children using ICS. There existed significant seasonal differences in asthma control. In observational studies assessing asthma control, it is therefore important to calculate long-term asthma control (instead of using current asthma control as indicator) or to stratify at least for seasonal variation.

P4818

Poor adherence to inhaled corticosteroids in childhood asthma: Don't blame (only) the patient

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Introduction: In population studies, the adherence to inhaled corticosteroid (ICS) treatment in asthma is usually poor. We previously showed high adherence to ICS in our paediatric asthma clinic, and this was related to parental illness and medication beliefs. The aim of the present study was to measure adherence and its determinants in children with asthma in primary care.
Methods: Children aged 2-6 yrs, who received a prescription for (ICS) by their general practitioner in the past year and who were still using ICS at the time of inclusion, were followed up for 3 months, during which adherence to ICS therapy was measured electronically by Smartinhaler®.
Results: 106 children (mean age 4.3 yrs) had had an ICS prescription over the past year. Parents of 95 children could be reached by telephone, 82 of whom were willing to provide information about current ICS use and symptoms of their child. 30 patients (36%) used ICS intermittently during symptomatic episodes, 24 (29%) patients used ICS for non-specific respiratory symptoms such as cough or for intermittent symptoms such as an isolated wheeze episode. 28 children (35%) were using ICS regularly, 21 of whom consented to electronic adherence measurement for 3 months. In these 21 patients, median adherence was 81% [range 34-97%] of prescribed dosages.
Conclusion: The low adherence to ICS in population studies of children with asthma may be partly explained by inappropriate prescription of ICS to children with intermittent episodes of wheeze, and non-specific respiratory symptoms such as cough. High adherence to ICS treatment was found in those patients who received ICS therapy in accordance with international asthma guidelines.

P4819

Lack of behavioural problems in preschool children using inhaled corticosteroids with high adherence

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Background: Parents of young children are frequently worried about the potential side effects of asthma treatment on their child's behaviour.
Aim: To examine whether preschool children using inhaled corticosteroids (ICS) for asthma are more likely to have more behavioural problems compared with healthy reference group.
Methods: We included 81 children 2-5 years of age with persistent asthma symptoms who were using ICS. During 3 months follow-up, adherence to ICS treatment was recorded by an electronical logging device (Smartinhaler®). The parents completed the Child Behaviour Checklist (CBCL) to assess behavioural problems; results were compared to published reference groups of healthy children.
Results: The median (interquartile range) adherence to ICS was 92 (78-97)%. There were no significant differences in CBCL scores (total, internalizing, externalizing problems) between children on ICS and healthy children (all p values > 0.2). Children with asthma were significantly more likely to have somatic complaints (p=0.001) and significantly less likely to have anxious/depressive symptoms (p=0.01) than the reference group.
Conclusions: Maintenance treatment with ICS, taken daily as prescribed, is not associated with an increased risk of behavioural problems in preschool children.

P4821

How much inhaled steroid is sufficient? Assessing the relationship between adherence rate to beclomethasone dipropionate and the level of asthma control

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Aims: To verify the relationship between adherence rate to beclomethasone dipropionate (BDP) and the level of asthma control.
Methods: In this prospective cohort study, 102 randomly selected subjects with persistent asthma, aged 4-14 years, were treated according to GINA recommendations and followed for one year. Adherence rate to BDP was measured through Doser CT® (Medtrack Products, USA), during each of the three follow-up visits taking place in the 4th, 8th and 12th month. Based on modified GINA categories, the level of asthma control was classified as either controlled or uncontrolled.
Results: Mild (36.2%) and moderate (56.9%) predominate over severe persistent asthma. The median adherence rate was higher in patients with controlled asthma during follow-up, but went down from 54.0% in the 4th month to 47.0% in the 12th month (p=0.038). Conversely, among patients with uncontrolled asthma, the median adherence rate reduced from 43.8% (4th month) to 31.2% (12th month, p=0.001). Multivariate analysis showed that the level of asthma control was independently associated to the adherence rate in all three visits (p-values ≤ 0.005).
Conclusion: In this study, level of asthma control was directly proportional to adherence rate. However, our results suggest that to gain control over mild and moderate persistent asthma, an optimal BDP adherence rate to currently recommended therapeutic regimens seems to be unnecessary.
Paulo Camargos is supported by FAPEMIG- Fundação de Amparo à Pesquisa do Estado de Minas Gerais, Brazil (Grant PPM-00230-10).

P4822

Fluticasone propionate/formoterol fumarate (FLUT/FORM) combination therapy has comparable efficacy to fluticasone propionate/salmeterol xinafoate (FLUT/SAL) in paediatric patients with asthma

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Background: A new asthma therapy combining FLUT/FORM in a single aerosol inhaler (*flutiform*®) has been shown to have comparable efficacy to FLUT/SAL (single inhaler) in adults. This study compared these combinations in a paediatric population.
Methods: Patients aged 4-12yrs (N=211) with mild/moderate persistent asthma were randomized 1:1 to 12 weeks of treatment with FLUT/FORM (100/10μg) or FLUT/SAL (100/50μg), twice daily, in an open-label, parallel-group, multicentre study. The primary endpoint was change in mean pre-dose FEV_1 values from Day 0 to Day 84. Secondary endpoints included change in mean FEV_1 values from Day 0 pre-dose to Day 84 120mins post-dose, discontinuations due to lack of efficacy and time to onset of action.
Results: FLUT/FORM was non-inferior to FLUT/SAL regarding change in LS mean pre-dose FEV_1: +182mL for FLUT/FORM and +212mL for FLUT/SAL (treatment difference: -31mL; 95% CI: -0.093, 0.031; per protocol set (PPS), FLUT/FORM: n=102; FLUT/SAL: n=99; Day 84). Non-inferiority of FLUT/FORM to FLUT/SAL was also demonstrated for post-dose FEV_1 values: change in LS mean post-dose FEV_1 was +308mL for FLUT/FORM and +325mL for FLUT/SAL (treatment difference: -17mL. 95% CI: -0.089, 0.055; PPS, n: as above). No patients discontinued due to lack of efficacy. No relevant differences in time to onset of action were evident between the two treatment groups.
Conclusion: Fluticasone/formoterol was comparable to fluticasone/salmeterol with regard to pre-dose and post-dose FEV_1 values and discontinuations due to lack of efficacy. FLUT/FORM and FLUT/SAL had comparable efficacy and safety profiles.

P4823

Long-term treatment with fluticasone propionate/formoterol fumarate (FLUT/FORM) combination therapy is well-tolerated and provides sustained effectiveness in paediatric patients with asthma

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Background: A new asthma therapy combining FLUT/FORM in a single aerosol inhaler (*flutiform®*) has been shown to be well-tolerated and effective in adolescents and adults over a 9 month period. This study examined the long-term safety and efficacy of FLUT/FORM in paediatric patients.
Methods: Patients aged 4-12yrs (N = 208) with mild/moderate persistent asthma received FLUT/FORM 100/10μg b.i.d. in a 24-week open-label, multicentre extension study. In the core study, patients had received 12 weeks of treatment with FLUT/FORM (100/10μg b.i.d.) or fluticasone propionate/salmeterol xinafoate (FLUT/SAL; 100/50μg b.i.d.). Safety was evaluated on the basis of adverse events (AEs), laboratory parameters, height and weight. The main efficacy endpoint was the change in mean pre-dose FEV_1 values during the extension study (from Day 84 to Day 252).
Results: The overall rate of AEs during the extension study (43.8%; n=208) was comparable to the core study treatment groups (FLUT/FORM: 44.2%, n=104; FLUT/SAL: 43.3%, n=104). The majority of AEs were mild, not considered study treatment related and did not result in withdrawal. Mean and median plasma cortisol values remained stable during the extension study, with no evidence of effects on normal growth (mean increases in weight and height were 2.1kg and 2.8cm respectively). Mean pre-dose FEV_1 increased by 105mL from 1.859L at the start of extension phase.
Conclusion: Long-term fluticasone/formoterol combination therapy has a good safety and tolerability profile and provides sustained effectiveness in paediatric patients with mild/moderate persistent asthma.

P4824

Salivary cortisol for assessment of hypothalamic-pituitary-adrenal (HPA) axis function in asthmatic children on inhaled corticosteroids (ICS)

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Background/Aim: Sampling for salivary cortisol (SC) determination is a pain free procedure and thus useful in the pediatric age group. Our aim was to compare Low Dose ACTH (LDST) salivary test with the classical blood test as well as the diurnal variation in salivary cortisol concentration for the assessment of HPA axis activity of asthmatic children on ICS.
Methods: LDST was performed in 62 asthmatic children (43 males, median age 7.9 yrs) before and after 3 months treatment with ICS. During the test, samples for SC were obtained simultaneously with serum samples (at 0-30-60 min). Patients sampled their own saliva between 09:00 and 21:00 hours (every three hours) for a whole day before and after treatment.
Results: A significant positive correlation was found between salivary and serum cortisol levels at 0' 30' and 60' after ACTH administration (R:0.818, $p<0.001$). Circadian rhythm cortisol parameters: cortisol awakening response, mean level and range of diurnal changes, correlated with serum cortisol at 60'(R:0.308, $p<0.025$; R:0.316 p=0.022; R:0.318, p=0.026) and SC at 0' (R:0.398, p=0.003; R:0.401, p=0.002; R:0.356, p=0.01), 30' (R:0.402, p=0.002; R:0.385, p=0.003; R:0.404, p=0.003) and 60' (R:0.303, p=0.041; R:0.368, p=0.009).
Conclusion: The salivary low dose ACTH test yields results that parallel the response of serum cortisol to ACTH and may provide an alternative to the blood test for HPA axis function evaluation. Diurnal SC variation may offer a dynamic evaluation over a day with none intervention.

P4825

The oral corticosteroid sparing effect of omalizumab in patients with severe chronic asthma: Is there a difference when you become 12 years old?

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Omalizumab is licensed for treatment of severe persistent allergic asthma over the age of 6 years. In England and Wales, the National Institute of Clinical Excellence recommends omalizumab as a possible treatment for young people over the age of 12, but not for children age 6 – 12.
We describe a population of children with severe asthma who have undergone a 16 week open label therapeutic trial of omalizumab.
The dose of oral corticosteroids at the start & end of the trial was documented. Some children completed modified quality of life and asthma symptom control questionnaires before and after the trial.
To date 15 children (13 boys) age 3-11 years, and 19 children (12 boys) age 11-16 years have completed a therapeutic trial in our centre. The baseline IgE was comparable between groups. We were able to reduce the daily corticosteroid dose in 13 children < 12 years (median pre 20, post 10 mg $p<0.01$) and in 16 children >12 years (median pre 10, post 5 mg, $p<0.01$).There was a significant increase pre- to post- trial in documented quality of life, using AQLQ (<12 n=8, >12 n=16), and asthma control (<12 n= 8, >12 n= 15) in all bar 1 patient in each group.
In conclusion, the use of omalizumab in children with severe asthma may result in a clinically significant decrease in the use of oral corticosteroids and an improvement in quality of life and a reduction in asthma symptoms. In our practice omalizumab was as effective in children <12 years of age as in the older age group. A placebo controlled randomised control trial of omalizumab using steroid sparing as primary outcome in a paediatric population is urgently required.

P4826

Safety and efficacy of omalizumab in children with allergic asthma

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Background: Omalizumab (Xolair) is a humanized monoclonal antibody used in the treatment of adults and children over 12 years with moderate to severe allergic asthma. Pediatric studies are few.
Objective: A retrospective chart review of pediatric patients who received omalizumab in the past 10 years for asthma at Nationwide Children's Hospital, Columbus, Ohio.
Results: We had 13 patients, M:F 7:6, median age 13 years (range 9-17), median duration of therapy 36 months (range 1 to 59 months), 9 African American and 4 Caucasian, duration of asthma 15 years (8 to 16). Eight are still on therapy. All patients had severe persistent asthma. Twelve patients were receiving combination therapy (ICS and LABA). Only 4 patients claimed compliance with their asthma controller therapy. Five had family history of asthma, 6 had smoking exposure. Median IgE before starting omalizumab was 249 (range 78 to 2600). Mean BMI was 25.7 and 46% of the patients were above the 100 percentile for BMI. Comparing between one year before and during omalizumab, mean hospital admission/patient/year decreased from 1.7±2.4 to 0.58±1.4 ($p<0.05$). There was also a trend towards improvement in ED visits from 2.3±3.2 to 1.7±3. Mean FEV1 during one year before omalizumab therapy, at initiation of therapy and during therapy was 91±18, 94±17, and 93±11 and was not statistically different. Two of 13 patients were taken off omalizumab because of serious side effects, one with anaphylaxis and second with dilated cardiomyopathy. Anaphylaxis was noted on first dose and cardiomyopathy was diagnosed in 5th year on therapy.
Conclusion: Omalizumab is add-on therapy for some patients with allergic asthma. Adverse reactions in children are limiting factor.

P4827

WITHDRAWN

P4828

Effect of leukotriene receptor antagonist on expression and variation of TGF-beta in T lymphocyte for mild persistent asthma in children

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Objective: To investigate the role of TGF-β_1 and action of montelukast (MT) in the pathogenesis of asthma in children.

Methods: A single-blind, placebo-controlled trail was conducted in 60 mild persistent asthma children (5-14 y). Patients were randomly assigned to receive 5mg MT or placebo for 12 weeks. 30 healthy children (5-14 y) were as control. Clinical and pulmonary function were assessed before and after treatment. The mRNA expression of TGF-β_1 in PBMC cells, subtypes of $FoxP_3^+CD_4^+$ T cells and TGF-β_1 in plasma were measured.
Result: After treatment, symptomes were improved with signigicant increase in pulmonary function in asthmatic, MT superior to placebo ($p<0.05$). The mRNA expression of TGF-β_1 and TGF-β_1 level in asthmatic were lower than that in control (0.312 ± 0.07 vs 0.607 ± 0.2, $p<0.05$ and 0.445 ± 0.13 vs 0.32 ± 0.04, $p<0.05$, respectively). Total $FoxP_3^+CD_4^+$ cell and $CD_{45}RA^+Foxp_3^{lo}$ were higher in asthmatic ($8.3\%\pm1.3\%$ vs $6.05\%\pm1.8\%$, $p=0.007$ and $4.60\%\pm1.04\%$ vs $3.27\%\pm1.03\%$, $p=0.011$, respectively). $CD_{45}RA^-Foxp_3^{hi}$ was lower ($0.75\%\pm0.13\%$ vs $0.93\%\pm0.26\%$, $p=0.021$). After treatment, $CD_{45}RA^-Foxp_3^{hi}$ was increased in MT compared to placebo group ($1.16\%\pm0.24\%$ vs $0.89\%\pm0.22\%$, $p=0.01$). TGF-β_1 levels had no correlation with those levels of pulmonary function.
Conclusion: The expression of TGF-β_1 was low in asthmatic children. Insufficient secretion of TGF-β_1 and the defection in activating $FoxP_3^+CD_4^+$ Treg cells might play an important role in pathogenesis of asthma. Up-regulation of expression of TGF-β_1 and induction of expression of $CD_{45}RA^-Foxp_3^{hi}$ in $Foxp_3^+CD_4^+$Treg cells by MT may be one of the mechanisms by which airway inflammation is inhibited in asthma.

P4829
Did inappropriate delivery systems hamper therapeutic efficacy of di-sodium-cromo-glycate (DSCG)? Time for a reappraisal
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Chymase-positive mast cells located in distal airways play a crucial role in asthma (Balzar 2005 & 2010). A review on inhaled DSCG by Keller & Schierholz (2011) provided evidence that poor efficacy of DSCG is most probably linked with subtherapeutic lung doses. The hygroscopic nature of DSCG causes particle growth associated with reduced lung deposition (Hiller 1980) which may explain insufficient therapeutic efficacy. Significantly higher in-vitro respirable doses were found by aerodynamic particle size assessments in a next generation impactor operated at 50% and 95% rel. humid., respectively using small droplet nebulisers compared to Intal® MDI and DPI (Keller 2007). Nebulised isotonic solutions provided better tolerability and efficacy than hypotonic Intal solution (Weiner 1988, Soferman 1990). Higher Cmax and AUC values were obtained for nebulisers compared to MDIs and DPIs (Patel 1986 & Kato 1999). Above mentioned aspects and critisism on earlier meta-analyses by Stevens 2007 were still ignored in the latest Cochrane meta-analysis by van der Wouden 2009. Recent data from a clinical trial in 48 asthmatic children (10.3 ± 2.8 yrs, 19 girls) inhaling for 6 months either 3× daily 20 mg isotonic DSCG via an investigational eFlow® electronic nebuliser or twice daily inhaled steroids via MDI with spacer showed comparable efficacy to inhaled steroids (Basek 2010). In conclusion, in-vivo data suggest that DSCG is a safe and effective asthma controller when a highly efficient, small droplet size generating nebuliser is used. Impactor data obtained at 50% and 95% rel. humidity show that therapeutic efficacy of DSCG is strongly affected by the delivery system.

P4830
Designing a holding chamber mask using anthropometric data and CAD-simulation
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Background: A good seal is regarded as critical factor of face-masks for efficient inhaled drug delivery. Dead space, contour, flexibility and acceptance are also important.
Objectives: Evaluate anthropometric data and CAD-simulation to optimise face-masks for inhalation.
Methods: Basic anthropometric data of faces and heads from 32 children (age 1,1-3,5 yrs) were determined with measuring tape and calliper. Data were compared to existing literature data. Frontal and profile photos were taken with and without a mask prototype. Photogrammetry was used to generate a 3-D CAD-database comprising the anthropometric and mask related information. The complex interactions between face and mask were then simulated and geometric data for optimised mask design determined. In a subsample (n=8) of the study population, fit of the optimised masks was visually controlled.
Results: Basic anthropometric data of the sample population agreed well with literature values, proving the study population to be representative. CAD-simulation identified the 2D-tightness geometry as inappropriate and was changed to a 3D-shape with soft lip seals. Dead space could be minimised yet leaving enough space for the nose to keep the mask comfortable. Design according to the CAD-simulation led to an optimised fit of the face mask. Dimensions went very well with the children's face structures. Enclosure of mouth and nose were both collision-free and space-saving.
Conclusions: Complex interactions between face and mask could be successfully simulated with a CAD-database. This helped to design face masks (PARI *SmartTouch*) which now allow for less leakage, more comfortable fit and minimised dead space - supporting efficient aerosol delivery.

P4831
Breath-by-breath delivered dose comparison from three anti-static valved holding chambers with facemasks under simulated pediatric breathing conditions
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Facemasks serve as a patient-device interface to facilitate drug delivery from a pressurized metered dose inhaler (pMDI) with an attached valved holding chamber (VHC), and are capable of significantly affecting inhalation drug therapy. A novel horizontal test rig designed for the evaluation of facemask performance under simulated conditions was used to measure delivered dose from ProAir HFA pMDIs (108 µg albuterol sulfate/actuation, Teva Specialty Pharmaceuticals LLC). Three brands of VHC-facemask systems were tested: preproduction OptiChamber Diamond (Diamond) VHCs with preproduction LiteTouch facemasks (Philips Respironics), AeroChamber Plus Z Stat (Z Stat) VHCs with ComfortSeal facemasks (Monaghan Medical Corp.), and Vortex VHCs with Spinner Duck facemasks (PARI GmbH).
A face replica of a four-year-old child, with a replaceable aerosol filter in the "mouth", was connected to a breathing simulator (ASL 5000; IngMar Medical Ltd) to simulate a pediatric breathing pattern (Vt=155 mL, f=25 bpm I:E=2:3). Each VHC-facemask system was naturally positioned against the face replica with a constant applied force supplied by a mass of 1.9 kg. Albuterol sulfate was quantified using HPLC after 1, 2, 4 and 8 "breaths" following pMDI actuation.

Table 1. Mean dose recovered on filter (%, n=3)

Total number of breaths	Diamond-LiteTouch system	Z Stat-ComfortSeal system	Vortex-Spinner Duck system
1	49	19	4.9
2	65	26	1.4
4	65	33	5.8
8	63	34	9.3

The delivered dose using the Diamond-LiteTouch system, after 1 breath, was significantly higher than the delivered dose using the Z Stat-ComfortSeal or the Vortex-Spinner Duck system after 8 breaths ($p<0.01$).