94. Drug delivery and pharmacokinetics I

P820
The effect of ketoconazole on the pharmacokinetics (PK) and pharmacodynamics (PD) of inhaled fluticasone furoate (FF) and vilanterol (VI) administered in combination in healthy subjects
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Rationale: A combination of the novel corticosteroid FF and long acting beta_2-agonist VI administered via dry powder inhaler (FF/VI) is being developed as a once-daily treatment for asthma and COPD. Both FF and VI are predominantly metabolised via CYP3A4 and their PK and PD could be affected by CYP3A4 inhibition.

Objective: To investigate the effects of the strong CYP3A4 inhibitor ketoconazole on the PK and PD of FF and VI.

Methods: Double-blind, randomised, placebo (P)-controlled, repeat dose, two-way crossover study. Healthy male and female subjects [N=18] received once daily oral ketoconazole (400mg) or P for 11 days with FF/VI (200/25mcg) for the final 7 days. PD and PK data were obtained up to 48h following the Day 11 dose.

Results: Co-administration of ketoconazole and FF/VI had no effect on 0-4h maximum heart rate or minimum blood potassium (treatment difference [90%CI] -0.6bpm [-5.8, 4.5] and 0.04mmol/L [-0.03, 0.11], respectively) whilst there was a measurable but clinically insignificant decrease in 24h weighted mean serum cortisol (treatment ratio [90%CI] 0.73 [0.62, 0.86]). Co-administration of ketoconazole increased (percent change [90%CI]) FF AUC(0-24) and Cmax by 36% [16, 59] and 33% [12, 58] and VI AUC(0 t') and Cmax by 65% [38, 97] and 22% [8, 38], respectively. Both treatments were well tolerated and there were no serious adverse events or withdrawals.

Conclusion: Co-administration of FF/VI with ketoconazole resulted in a less than two-fold increase in systemic exposure to FF and VI with no clinically significant systemic effects.

Funded by GSK (HZA105548; NCT01165125)

P821
Vilanterol, a novel inhaled long-acting beta_2 adrenoceptor agonist (LABA), demonstrates extensive first pass clearance to metabolites with negligible pharmacological activity in man
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Introduction: Vilanterol (VI) trifenate is a novel LABA with demonstrated 24-hour clinical duration of action, currently in development in combination with an inhaled corticosteroid for once-daily treatment of COPD & asthma.

Objectives: The excretion and metabolism of radio-labelled VI was investigated following oral dosing to represent the swallowed portion of an inhaled dose.

Methods: Open label, single dose study. Healthy male subjects [N=6] received an oral solution dose of 200 ug of [14C]VI (2 uCi). Plasma samples and all urine and faeces were collected up to 168 h post dose and analysed for total radioactivity, VI and VI metabolites (as appropriate).

Results: VI was well absorbed (>50% of the radioactive dose). VI represented a very small percentage (<0.5%) of the total circulating drug-related material in the plasma indicating extensive first-pass metabolism of VI. In total 70% of the recovered radiolabel was collected in the urine with the remainder recovered in the faeces. The primary route of clearance of VI was via O-dealkylation to pharmacologically inactive metabolites which were predominantly excreted in the urine. VI was well tolerated with no notable changes in heart rate, serum potassium and glucose levels or ECG parameters.
Conclusion: VI undergoes extensive first-pass metabolism in man. VI was well tolerated after an oral dose (200 μg) considerably in excess of the likely clinical inhalable dose (25 μg), indicating absent pharmacological activity of the metabolites in man (in agreement with pre-clinical data).

Funded by GSK (B2C106181; NCT01286381)

P822 Safety, pharmacokinetics (PK) and pharmacodynamics (PD) of single doses of GSK961081 OD (V) in patients with COPD

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Introduction: GSK573719 is a new LAMA, in patients with COPD

Methods: In a randomised, double-blind, dose-ascending, 4-way crossover study, 24 patients enrolled received single doses of 4 of the following 5 treatments by dry powder inhalation: GSK573719 (250/500/1000 μg) placebo (PBO), tiotropium bromide (TB): (18μg). Doses were separated by 14 days.

Results: 20 patients completed all dosing periods. Acute adverse events (AEs) were reported with 31–41% GSK573719, 38% TB and 29% of PBO doses, most of mild or moderate intensity. There were 5 severe AEs and 4 patients withdrew due to AEs (none were drug related). No clinically meaningful differences in clinical chemistry, vital signs or ECG parameters were seen for GSK573719 vs PBO, although lower heart rates were observed for all active treatments (up to 7.2% lower with 1000 μg vs PBO). GSK573719 was rapidly absorbed (median tmax 5–15min), but 40–61% of plasma PK samples were nonquantifiable. Urine t 1 dose was on average 11–12h. Specific airway conductance (sGaw) and FEV1 responses were significantly higher for all active treatments vs PBO, and responses for all GSK573719 doses were higher than TB. No correlation was observed between GSK573719 systemic exposure and PD variables.

Conclusion: Single doses of GSK573719 250–1000μg were well tolerated and associated with clinically relevant improvements in lung function in COPD patients.

Funded by GSK (AC4108123; NCT00515502)

P823 The pharmacodynamics of GSK961081 in patients with COPD

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Introduction: GSK961081 is a dual pharmacophore with both muscarinic antagonist and beta2 agonist (MABA) activity.

Objectives: To assess the pharmacodynamics of GSK961081.

Methods: This was a randomised, double-blind, double-dummy, placebo-controlled, incomplete block crossover study in 50 COPD patients. Patients were randomised to 3 of 4 possible treatments: 400 μg GSK961081 OD (n=32); salmeterol 50 μg dose) and dry mouth (n=1, 1200 μg dose), or QTcF 0–4h after the final dose of any active treatment vs placebo. There was no significant difference in maximum change from baseline heart rate, glucose or QTcF 0–4h after the final dose of any active treatment vs placebo. The inhalation resulted in a linear PK for lysine salt via nebulizer, with/without concomitant charcoal intake (all subjects also assumed orally a 500mg dose). The inhalation resulted in a linear PK for GSK573719 systemic exposure and PD variables.

Results: A statistically significant decrease was observed for serum IL6 and IL8 and sputum TNFα and IL-8 concentrations for all active treatments vs placebo (p<0.001). There was a small decrease in potassium 0–4h after the final dose of all active treatments. The adverse event profile for all active treatments was similar to placebo.

Conclusion: Administration of FF and VI in combination was not associated with an increase in systemic exposure or systemic pharmacodynamic effects compared with administration of either compound alone.

Funded by GSK (HZA105871; NCT00538057)

P824 The safety, tolerability, pharmacodynamics and pharmacokinetics of inhaled fluticasone furoate (FF) and vilanterol (VI) are unaffected by administration of aspirin in patients with asthma and COPD

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Introduction: A combination of the novel corticosteroid FF and long acting beta2-agonist VI (FF/VI) is currently under development as a once-daily inhalation treatment for asthma and COPD.

Objectives: To assess whether the pharmacodynamics (PD) and pharmacokinetics (PK) of FF and VI are affected when delivered as the FF/VI combination in comparison with FF and VI administered from the same novel dry powder inhaler.

Methods: Single centre, randomised, double-blind, placebo-controlled, four-way crossover study. Healthy male and female subjects [N=16; 21–57 years] received single super-therapeutic doses of FF (800μmcg), VI (100mcg), FF/VI (800/100mcg) and placebos. PK and PD were monitored post-dose.

Results: FF/VI decreased serum cortisol (0-24h weighted mean vs placebo) by 14.7±% vs 24.1% for FF alone; the difference of 12.3% (90% CI: 4.4, 20.9) was considered non-inferior (defined as lower CI > -20%). FF/VI increased heart rate (+0.19±0.10 vs placebo) by 2.78±mm vs 6.99±mm for VI alone; the difference of 1.29±0.89 (90% CI: -4.6, 2.1) was considered non-inferior (defined as upper CI < +10.89mm). There were no differences in minimum blood potassium (0-4h). FF and VI were well tolerated, with no differences in safety, PK and PD variables.

Conclusion: Delivery of FF/VI is well tolerated and associated with clinically relevant improvements in lung function in COPD patients.

Funded by GSK (HZA105871; NCT00538057)

P825 Aspirin inhalation treatment for COPD patients: Preliminary studies on PK and inflammatory biomarkers

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We are currently investigating if the use of aspirin (ASA), administered via inhalation, can exert a local anti-inflammatory effect, to propose it as a treatment for COPD, an inflammation-related pathology.

As little is known on inhaled ASA’s PK, a 3-way crossover study was performed on 14 moderate COPD subjects, which were administered 250/500/650mg of ASA’s b.i.d via nebulizer, with/without concomitant charcoal intake (all subjects also assumed orally a 500mg dose). The inhalation resulted in a linear PK for ASA and salicylic acid in plasma. Variability appeared important after inhalation, while modest after oral intake. Only approximately 10% of the administered dose was recovered in urine (70% after oral dose).

The efficacy of inhaled ASA was investigated in 4-week placebo-controlled clinical trial performed on 59 moderate COPD subjects, who inhaled 250, 500 or 750mg of ASA BID. Functional respiratory parameters were measured together with inflammatory markers in serum and induced sputum.

A statistically significant decrease was observed for serum IL6 and IL8 and sputum TNFα (trend test: 0.0004, 0.0144 and 0.0275). The 250mg dose was observed to statistically increase FEV1 and FEV/FVC from T0 to T4 (p<0.02 and 0.008). The same dose also showed important effects, compared to placebo, both on inflammation (reduction of sputum neutrophil elastase, p<0.01) and sputum production (p<0.008). These results are not conclusive to prove the efficacy of the treatment (large intra-patient variation, lack for specific biochemical marker for COPD).

However, also considering the good tolerability, they support the opportunity for a larger clinical trial.

P826 Pharmacokinetic bioequivalence of inhaled CHF 1535 50/6 vs. the free combination of beclomethasone and formoterol in asthmatic children

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Introduction: To develop a new fixed formulation of Beclomethasone dipropionate (BDP) 50 μg and Formoterol fumarate 6 μg (CHF 1535 50/6) delivered via a pMDI for treatment of children with severe asthma.

Rationale: To develop a new fixed formulation of Beclomethasone dipropionate (BDP) 50 μg and Formoterol fumarate 6 μg (CHF 1535 50/6) delivered via a pMDI for treatment of children with severe asthma.
Objective: To investigate pharmacokinetic of B17MP (active BDP metabolite) and Formoterol in children with asthma after inhalation of CHF 1535 50/6 vs. the licensed free combination of BDP and Formoterol dispensed with AeroChamber Plus™.

Methods: 22 children (5-11yrs) with mild asthma were included in this open-label, randomised, 2-way cross-over study of inhaled BDP 200µg and Formoterol 24µg. Eight-hour pharmacokinetic profiles (Cmax and AUROCt) for B17MP and Formoterol after single inhalation were primary endpoints evaluated by analysis of variance and 90% bioequivalence limits.

Secondary endpoints were pharmacodynamics: serum potassium, heart rate, and cortisol excretion.

Results: B17MP and Formoterol pharmacokinetic parameters showed comparable values and the upper limit of the 90% CI was well within the bioequivalence limit. The pharmacodynamic parameters also showed similar values after both treatments.

Conclusion: After CHF 1535 50/6 administration, the BDP and Formoterol treatments.

Limit. The pharmacodynamic parameters also showed similar values after both treatments.

Objective: To investigate the space- and time-related distribution pattern of budesonide aerosolized via MDI.

Methods: A matrix of crystallization dishes was set up in a measurement chamber. One puff of budesonide MDI (184 µg nominal dose, 200 µg nominal dose) was aerosolized and aerosol was allowed to sediment for 0.25 to 6.5 hours. Recovery of budesonide in the crystallization dishes was measured via HPLC and correlated to time course and spatial matrix.

Results: In 1 m distance of actuating the MDI, a mean recovery of budesonide of 0.688 µg after 0.25 hours and 1.423 µg after 6.5 hours was observed. The surface concentration at 1 m distance was 9.7 ng/cm² after 0.25 hours and 20.1 ng/cm² after 6.5 hours.

Conclusion: This study is a valid basis for risk assessment of carry-over effects in clinical trials with aerosolized drugs. Regarding surface concentrations in the nanogram range as shown in our study compared to serum drug concentrations in the picogram range as determined in pharmacokinetic trials, carry-over effects via aerosols seem improbable. Further studies to determine the extent and origin of these effects will therefore be performed.

P828 Fluticasone/salmeterol combined in the new Forspiro® inhaler is as effective and safe as Seretide® Accuhaler® in adult and pediatric asthmatics

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Background: Contamination and carry-over by active drug components is a major issue, especially in pharmacokinetic studies carried out with aerosolized substances. Measures to avoid contamination and carry-over in blood samples remain poorly standardized and validated.

Objective: To investigate the space- and time-related distribution pattern of budesonide aerosolized via MDI.

Methods: A matrix of crystallization dishes was set up in a measurement chamber. One puff of budesonide MDI (184 µg nominal dose, 200 µg nominal dose) was aerosolized and aerosol was allowed to sediment for 0.25 to 6.5 hours. Recovery of budesonide in the crystallization dishes was measured via HPLC and correlated to time course and spatial matrix.

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P829 Effect of systemic and extra-fine particle inhaled corticosteroids on corrected alveolar nitric oxide (CANO) in COPD

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Background: Contamination and carry-over by active drug components is a major issue, especially in pharmacokinetic studies carried out with aerosolized substances. Measures to avoid contamination and carry-over in blood samples remain poorly standardized and validated.

Objective: To investigate the space- and time-related distribution pattern of budesonide aerosolized via MDI.

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Results: In 1 m distance of actuating the MDI, a mean recovery of budesonide of 0.688 µg after 0.25 hours and 1.423 µg after 6.5 hours was observed. The surface concentration at 1 m distance was 9.7 ng/cm² after 0.25 hours and 20.1 ng/cm² after 6.5 hours.

Conclusion: This study is a valid basis for risk assessment of carry-over effects in clinical trials with aerosolized drugs. Regarding surface concentrations in the nanogram range as shown in our study compared to serum drug concentrations in the picogram range as determined in pharmacokinetic trials, carry-over effects via aerosols seem improbable. Further studies to determine the extent and origin of these effects will therefore be performed.

P830 Lung deposition of the extra fine dry powder fixed combination beclometasone dipropionate plus formoterol fumarate via the NEXT DPI® in healthy subjects, asthmatic and COPD patients

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Background: Chiesi has developed the new pocket size, medium air flow resistant, breath actuated multidose-reservoir dry powder inhaler NEXT DPI®.

Objective: The lung deposition and distribution pattern of the extrafine fixed combination of beclometasone dipropionate 100µg and formoterol fumarate 6µg administered via the NEXT DPI® was assessed using a gamma-spectrometric technique after inhalation of a single dose of the 85Kr-radiolabelled combination (total dose BDP/formoterol 400/24µg).

Methods: 10 healthy subjects, 9 asthmatic patients (30%<FEV1<80%) and 9 patients with stable chronic obstructive pulmonary disease (COPD) (FEV1/FVC<70%, 30%<FEV1<50%) were treated according to an open, single dose design.

Results: Similar lung and extra-thoracic deposition were observed between the groups. The average lung deposition was 55% relative to the emitted dose in healthy subjects, 56% in patients with asthma and 55% in COPD patients. The extra-thoracic deposition was 43% in healthy subjects, 42% in asthmatic patients and 42% in COPD patients. The amount exhaled ranged between 1.6 to 3.3%.

Conclusion: Whilst CANO remains a biomarker of interest in COPD, it is not suppressed by systemic or extra-fine particle ICS. Hence CANO is unlikely to be a useful marker for monitoring response of small airway disease to therapies in COPD.

Abstract printing supported by Chiesi. Visit Chiesi at Stand D.30

139s
A novel NEXT DPI® dry powder inhaler and its use in asthma and COPD population

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Rationale: In asthma and COPD the dry powder inhalers (DPIs) facilitate patient’s compliance to drug intake. Chiesi Farmaceutici developed a new inhaler, NEXT DPI® which is pocket size medium-resistant-buffed mechanism (BAM) multidose-reservoir to be used for drug delivery.

Objective: To verify that the peak inspiratory flow (PIF) required for the drug delivery is not influenced by patient’s age and disease.

Methods: Children (n=27; age 5-11), adolescents (n=20; age 12-17) and adults (n=21; age ≥ 18) with asthma and COPD patients (n=21; age ≥ 20) were included in this multicenter open-label placebo study. After baseline pulmonary function assessments (FEV1, FVC; PIF tested with spirometer and In-Check Dual® device) patients inhaled through the NEXT DPI® test the BAM activation, checked by the residual doses in the dose-counter. Usability evaluation questionnaire, adverse events (AE) and vital signs were also recorded.

Results: In all patients, spirometry showed from moderate to severe airways obstruction. All patients, irrespective of age and disease, were able to activate the BAM. The mean PIF value (asthmatic patients: 10.4±4.20±6.6 L/min, range 40-120; COPD patients: 97.9±18.8 L/min, range 51-120) measured with the In-Check was greater than the threshold set for the BAM activation and not influenced by age and disease severity. No patients had problem in using the NEXT DPI® correctly. A total of 7 AE were reported in 5 patients, no one related with the use of NEXT DPI® or severe in intensity. No Severe Adverse Events were reported.

Conclusions: NEXT DPI® can be easily used and activated in a wide population of asthmatics and COPD patients irrespective of age and disease severity.

Efficiency of ipratropium bromide and salbutamol deposition in the lung delivered via a soft-spray inhaler or chlorofluorocarbon metered-dose inhaler

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Purpose: The dose combination of ipratropium bromide (Ip) 42 mcg and albuterol (Alb) 200 mcg, propelled by CFC, is currently marketed in a single canister dosag form. A soft-spray, aqueous solution-based delivery system of this combination was developed. This pharmacokinetic study compared the efficiency of a soft-spray delivery of the combination to the lung compared to CFC delivery.

Methods: Pulmonary pharmacokinetic substudy comprised of 278 patients was conducted from two trials differing only by doses evaluating Ip and Alb delivered via the soft-spray inhaler or CFC-MDI in 2,578 patients. Ip alone delivered via the soft-spray inhaler and placebo delivered via the CFC inhaler was used as controls. LCM/MS/MS assays for analytes were developed for plasma and urine biofluids.

Results: Comparing AUC, Cmax, and Cmin showed that systemic exposure to Alb and Ip delivered via the soft-spray inhaler was proportional to the doses delivered. Comparability was obtained when comparing the soft-spray inhaler-delivered Ip at half the dose of the CFC-MDI. Since Ip is not significantly absorbed from the gastrointestinal tract, the systemic exposure observed is a relevant marker for lung deposition. Ip alone gave equivalent exposure as the combination demonstrating a lack of interaction.

Conclusions: These systemic exposure analyses can be regarded as a marker of lung deposition and therefore demonstrate that the soft-spray inhaler delivers drug more efficiently to the lung than CFC-MDI.

Maintenance of lung function and asthma control with extrafine beclomethasone/formoterol

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Introduction: Asthma management focuses on achieving and maintaining asthma control. Very few studies have assessed whether complete and sustained asthma control is maintained after switching ERS/ALBA fixed combinations in clinical practice.

Aim: To demonstrate equivalence between equipotent doses of extrafine BDPF pMDI and Beclomethasone/salmeterol (PFS) (Diskus®) in maintaining lung function and asthma control.

Methods: Prospective, double-blind, double-dummy, randomized, parallel group, controlled trial. 416 asthma patients controlled on FFS 500/100μg/day (Diskus®), pMDI or separate inhalers were randomized to 12-week treatment withextrafine BDPF 400/24μg/day pMDI or PFS 500/100μg/day (Diskus®). Pre-dose FEV1 was the primary outcome, secondary outcomes included asthma control (ACQ-7).

Results: At the study end, pre-dose FEV1 was equivalent between treatments (difference between means 0.01 L; 95% CI -0.03 to 0.06 L) with no changes from baseline in both groups. ACQ-7 score was equivalent between groups (Table 1). Post-dose FEV1 in the first hour was significantly higher for extrafine BDPF pMDI both at baseline and after 12-week treatment (Fig. 1, Table 1). No safety issues were reported in both groups.

Conclusions: Patients previously controlled with FIFS in any device formulation can safely switch to extrafine BDPF pMDI and maintain an equivalent asthma control with a sustained faster onset of action.

GSK573719 inhalation powder, a new long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD)

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Introduction: GSK573719 is a new long-acting muscarinic antagonist offering sustained 24-hour bronchodilation in development for the treatment of COPD.

Objectives: To evaluate the safety, tolerability and pharmacokinetics of inhaled GSK573719 in a new dry powder (DP) formulation in COPD patients.

Methods: In this randomised, double-blind study, 38 patients with COPD received GSK573719 (250 g, n=20; 1000 g, n=9) or placebo (n=9) via a novel DP inhaler (DP) once daily for 7 days.

Results: Of 43 adverse events (AEs) in 21 (55%) patients, 16 were drug related (all mild or moderate); placebo, 4 (headache, pruritus, flushing, hypoesthesia); GSK573719 250 g, 5 (arythymia, tachycardia, dyspnoea, hypertension, bronchospasm); GSK573719 1000 g, 7 (blood pressure increase, thirst, oropharyngeal pain, headache, dry mouth, dyspnoea, feeling abnormal). Of 3 AE-related with-drawals (chest pain, respiratory tract inflection, dyspnoea), only dyspnoea was considered drug-related (1000 g). The 1000 g dose showed larger increases than 250 g in heart rate (HR) (0–4 h) vs placebo, but 24-h Holter monitoring showed no dose effect over 24 h and the treatment effects were small. GSK573719 was rapidly absorbed (Cmax, 5-15 min); 1–2% of the total dose was excreted unchanged in the urine. Accumulation (Day 7) Day 1 was low: 1.5–1.9x based on plasma data (1.8-2.4, urine data). No correlation was seen between individual maximum HR (1.8-2.4) and GSK573719 Cmax.

Conclusions: GSK573719 250 g or 1000 g once daily by novel DP inhaler was well tolerated by patients with COPD.

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P835
Optimization of inhalation treatment – Evaluation of influence of PNEUlogic® and Optimiser® spacers on aerosol particle distribution from pMDI-EB
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Introduction: PNEUlogic® (PNL) is the first inhalation chamber [vol. 800 ml] integrated with the spacer, used for the controlled drug delivery from pMDI-EB. Optimiser® (OPT) [vol. 50 ml] is the aerosol chamber used for drug administration from pMDI-EB.

The aim of the study was to evaluate the influence of inhalation chamber and method of performing inhalation on the quality of aerosol.

Method: Aerosol particle distribution and mass of aerosol was measured using particle counter with constant flow of 28,3L/min.

Results: Results are shown in Table 1 and Table 2.

Table 1: Results shown in Table 1 and Table 2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>PNL</th>
<th>PNL-X</th>
<th>OPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMAD (μm)</td>
<td>7.49</td>
<td>5.96</td>
<td>4.17</td>
</tr>
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<td>Mass of aerosol (μg)</td>
<td>0.2574</td>
<td>0.1834</td>
<td>0.0129</td>
</tr>
</tbody>
</table>

X = exhalation prior to the drug delivery into the chamber.

Table 2: Results shown in Table 1 and Table 2.

<table>
<thead>
<tr>
<th>Drug</th>
<th>PNL</th>
<th>PNL-X</th>
<th>OPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMAD (μm)</td>
<td>4.18</td>
<td>3.26</td>
<td>4.83</td>
</tr>
<tr>
<td>Mass of aerosol (μg)</td>
<td>0.0313</td>
<td>0.0194</td>
<td>0.0862</td>
</tr>
</tbody>
</table>

X = exhalation prior to the drug delivery into the chamber.

Our study demonstrated statistically significant influence of chamber’s size and the exhaled air into the chamber on quality and mass of aerosol.

Conclusion: Application of the chamber integrated with the spacer opens up new possibilities for optimization of inhalation treatment.

P836
In vitro comparison of aerosol characteristics of HFA ipratropium bromide pressurized metered dose inhaler (pMDI) formulation from three valved holding chambers (VHCs)
Kurt Nikander1, Loss Slater2, Dirk von Hollen1, Ross Hatley2. 1Philips Respironics, Respironics New Jersey, Inc., Parsippany, NJ, United States; 2Respiratory Drug Delivery (UK) Ltd, Chichester, United Kingdom

Inhaled bronchodilators and anticholinergics are the mainstay in the management of patients with chronic obstructive pulmonary disease. This study compared the in vitro aerosol characteristics from an HFA ipratropium bromide pMDI (Atrovent, g ipratropium bromide, Boehringer Ingelheim Ltd) with two anti-static VHCs, a preproduction OptiChamber (iChamber (Diamond, Philips Respironics) and an Aeroneb Plus Z-Sta (Z-Sta, Monaghan Medical Corp.) VHC, and the pMDI alone.

Six pMDIs were primed before use and six of each VHC were washed and air-dried for 20 s extraction at 30 L/min, repeated 10 times. Drug deposits from the NGI were impacted using the NGI (for pMDI alone - tested before and after VHC tests), followed by a preproduction OptiChamber Plus (AO +, Monaghan Medical Corp.) VHC, and the pMDI alone.

Potential throat deposition compared to the pMDI alone.

P837
Airway humidity during oxygen therapy: Impact of humidification and applicator design
Markus Wenzel, Dominic Dellweg, Ekkehard Hohn, Olaf Bourgand, Peter Haaf. Pneumologie, Fachkrankenhaus Kloster Grafchaft, Schmallenberg, NRW; Germany

Background: Stationary oxygen therapy is usually combined with a humidification device in order to prevent mucosal dryness. The impact of the applicator design on airway humidity however has not been investigated to date.

Rationale: To investigate the impact of oxygen applicator design on airway humidity.

Method: First we developed a sampling and analysis system with a heated sampling probe to measure humidity of air samples under standard conditions during the inspiratory cycle. We measured 12 individuals with an intranasal (standard nasal cannula) and pre-nasal (Oxynasor) applicator at different flow rates with and without humidification devices. The Oxynasor device is characterized by a cyclic effect of the emitting gas which reduces the oxygen velocity at the outlet.

Results: Intra-nasal humidity dropped significantly from 40.3±6.7% to 29.0±6.8% at a flow rate of three litres when oxygen was given intranasally without humidification (p<0.01). We observed no significant change in airway humidity when oxygen was given prenasally with and without humidification.

Conclusion: We propose two mechanisms to be responsible for this phenomenon: First pre-nasal application with low outlet velocity of dry oxygen allows for absorption of humidity from the surrounding air prior to nasal entry and second intra-nasal application with a high exit velocity from the applicator system might dry out the nasal mucosa by means of convection. Nasal oxygen application with the Oxynasor device might obviate the need for humidification and therefore might simplify application and reduce therapy cost.

P838
Objective measurement of inhalation profiles in patients using metered dose inhalers (MDIs)
Wahida Azouz1, Philip Cheчетz2, Harold Hosker3, Dinesh Saralaya4, Henry Chrysten1. 1Pharmacy, University of Huddersfield, Huddersfield, United Kingdom; 2Heudatics, Leeds General Infirmary, Leeds, United Kingdom; 3Respiratory, Airedale General Hospital, Steeton, United Kingdom; 4Respiratory, Bradford Royal Infirmary, Bradford, United Kingdom

Subjective assessments of inhaler technique suggest that patients have problems using MDIs (Crompton et al. Respir Med 2006). To expand on this problem we have electronically measured inhalation profiles of patients when they use a MDI using their normal technique. Children with asthma (CHILD; n=20), adults with asthma (ADULT; n=60) and chronic obstructive airways disease (COPD; n=33) completed the study. We have measured their peak inhalation flow (PIFR), inhalation volume (IV), length of inhalation (TI) and the time between actuation and the start of an inhalation (TsIn). The results are shown in the table below.

Table 1. Results: Mean (SD) [range]

<table>
<thead>
<tr>
<th>Device</th>
<th>Child</th>
<th>Adult</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIFR (L/min)</td>
<td>0.89 (0.73) [0.02-2.73]</td>
<td>1.67 (0.91) [0.03-4.2]</td>
<td>1.06 (0.56) [0.14-2.67]</td>
</tr>
<tr>
<td>IPv (μg)</td>
<td>0.2574</td>
<td>0.1834</td>
<td>0.0129</td>
</tr>
<tr>
<td>MMAD (μm)</td>
<td>0.0331</td>
<td>0.0194</td>
<td>0.0862</td>
</tr>
</tbody>
</table>

Using a PIFR <90L/min for slow flow with a TsIn of 0.2 seconds for good coordination only 3 CHILD, 4 ADULT and 6 COPD demonstrated a good inhalation technique. The PIFR of 15 CHILD was <90L/min, 26 ADULT and 24 COPD. 9 CHILD actuated too early, 4 too late and 2 did not actuate. 17 ADULTS actuated too early, 27 were too late and 5 did not actuate. 9 COPD actuated too early and 14 too late. The mean (SD) ADULT ACQ was 2.04 (1.00) with a definitive at which it should be at a flow rate of three litres when oxygen was given intranasally without humidification (p<0.01). We observed no significant change in airway humidity when oxygen was given prenasally with and without humidification.

Conclusion: We propose two mechanisms to be responsible for this phenomenon: First pre-nasal application with low outlet velocity of dry oxygen allows for absorption of humidity from the surrounding air prior to nasal entry and second intra-nasal application with a high exit velocity from the applicator system might dry out the nasal mucosa by means of convection. Nasal oxygen application with the Oxynasor device might obviate the need for humidification and therefore might simplify application and reduce therapy cost.

P839
In-vitro nebulised dose emission characteristics of a tobramycin solution (75mg/ml) using an I-NEB (I-NEB) and a par LCV driven by a Turboboy compressor (PARI) nebuliser
Mohamed Yousef Khan1, Nicholas Powles2, Matthew Stirling2. 1Respiratory, Airedale General Hospital, Steeton, United Kingdom; 2Respiratory, Bradford Royal Infirmary, Bradford, United Kingdom

In practice solutions are nebulised by the equipment that is available rather that those that are recommended in the Summary of Product Characteristics (SPC). We have compared the in-vitro aerodynamic droplet characteristics of Bromabloc® when an in-vitro aerosol was nebulised by PARI (Pari GMBH), recommended in the SPC, and an I-NEB (Philips Respironics, UK) with a 300l/h cup. We have previously adapted the condensation methodology for nebulisers (Adelrahim & Chrystyn, J Aerosol Med 2009) and modified this to incorporate breath simulation (BS, tidal volume of 500ml and an inspiration: expiration ratio of 1:3) for use with I-NEB. The schematic design of our methodology is shown in figure 1.

The mean (SD) aerodynamic droplet characteristics of tobramycin nebulised using a PIFR <90L/min for slow flow with a TsIn of 0.2 seconds for good coordination only 3 CHILD, 4 ADULT and 6 COPD demonstrated a good inhalation technique. The PIFR of 15 CHILD was <90L/min, 26 ADULT and 24 COPD. 9 CHILD actuated too early, 4 too late and 2 did not actuate. 17 ADULTS actuated too early, 27 were too late and 5 did not actuate. 9 COPD actuated too early and 14 too late. The mean (SD) ADULT ACQ was 2.04 (1.00) with a definitive at which it should be at a flow rate of three litres when oxygen was given intranasally without humidification (p<0.01). We observed no significant change in airway humidity when oxygen was given prenasally with and without humidification.

In the I-NEB data the fine particle dose (FPD) is 8.3mg. Separate determina-

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nebulised using an I-Neb with a 300μl cup could be comparable to 4ml nebulised by a Pari LC+.

<table>
<thead>
<tr>
<th></th>
<th>PARI</th>
<th>I-NEB</th>
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<tbody>
<tr>
<td>Residual amount (mg)</td>
<td>202.8 (37.2)</td>
<td>5.5 (2.4)</td>
</tr>
<tr>
<td>Total emitted dose (mg)</td>
<td>119.1 (20.8)</td>
<td>15.5 (2.4)</td>
</tr>
<tr>
<td>Fine particle fraction (%)</td>
<td>64.9 (4.5)</td>
<td>53.3 (9.9)</td>
</tr>
<tr>
<td>Mass Median Aerodynamic Diameter (μm)</td>
<td>3.8 (0.3)</td>
<td>4.4 (0.2)</td>
</tr>
</tbody>
</table>