

TUESDAY, SEPTEMBER 27TH 2011

415. Airways disease comorbidities and general aspects

P3991**Systemic inflammation is enhanced by acute hyperglycaemia and suppressed by insulin in COPD**

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Introduction: Over half of COPD patients hospitalised for exacerbations have elevated blood glucose. Acute hyperglycaemia is associated with increased risk of death and prolonged hospital stay [Baker *et al* Thorax;61:284-9]. We investigated the effect of acute hyperglycaemia and insulin therapy on systemic inflammation.

Methods: 8 stable COPD patients (4male, 66±8yrs, FEV₁ 44±16%predicted) and 8 volunteers (8male, 24±5yrs, FEV₁ 89±12%) with fasting glucose <7mM received an octreotide infusion to inhibit pancreatic function. Glucose and insulin were infused for 4 consecutive 60min periods to achieve: Low glucose (fasting), low insulin (0.3mU.kg⁻¹.min⁻¹); high glucose (10mM above fasting levels), low insulin; high glucose, high insulin (1.5mU.kg⁻¹.min⁻¹); low glucose, high insulin. Cytokines were measured in blood sampled at the end of each 60min period using a Bio-Plex system (Bio-Rad).

Results: In COPD, high glucose, low insulin increased IP10 by 48 (12-181)% (median (interquartile range)), TNFa by 28 (8-54)% and IL-12 by 16 (2-34)% from low glucose, low insulin (p<0.05). IP10 increased significantly more in COPD than in volunteers (p=0.009). Subsequently, low glucose, high insulin suppressed IP10, TNFa and IL-12 to starting concentrations (p<0.05). Additionally low glucose, high insulin suppressed IL-1a, IL-1b, IL-16 and IL-4 by 4 to 26% (p<0.05). Suppression of IP10 and TNFa was significantly greater in COPD patients than in volunteers (p=0.038).

Conclusion: Acute hyperglycaemia amplifies systemic inflammation in COPD, which could be detrimental during exacerbations. The anti-inflammatory potential of blood glucose control with insulin for exacerbations requires further investigation.

P3992**Risks of diabetes mellitus and hyperglycaemic adverse events in patients with COPD taking inhaled corticosteroids**

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Background: A recent study of patients with lung disease and with prescriptions for inhaled corticosteroids (ICS) detected a 34% increased risk of diabetes mellitus.

Methods: A retrospective analysis evaluated the double-blind, controlled, clinical trials in COPD (duration >6 months), involving budesonide (BUD) or BUD/formoterol (8 trials, n=4616 for BUD; n= 3643 for non-ICS). Cox proportional hazards regression modelling, both adjusted and not adjusted by study, was used to estimate the relative effect of ICS on diabetes mellitus/hyperglycaemia adverse events (AEs) or serious adverse events (SAEs).

Results: The occurrence of diabetes mellitus/hyperglycaemia AEs was 1.3% for BUD and 1.2% for non-ICS (HR 0.99 [95% CI: 0.67-1.46], p=0.96); the occurrence of diabetes mellitus/hyperglycaemia SAEs was 0.1% for BUD and 0.03% for non-ICS. There was no increased risk with higher doses of BUD. The risk for diabetes mellitus/hyperglycaemia increased with increasing age, BMI and disease severity. Four trials (n=3329 for BUD; n= 2368 for non-ICS) included collection of blood glucose (non-fasting). No significant changes over time were observed for any treatment comparisons.

Conclusion: Treatment with BUD in patients with COPD was not associated with increased risk of diabetes mellitus or hyperglycaemia.

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P3993**The relationship between acidic & non acidic gastro esophageal reflux disease (GERD) and asthma**

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Asthma is a chronic airway disease characterized by airway constriction, inflammation, and hyper responsiveness to specific and non specific stimuli. GERD is a potential trigger of asthma. The relationship between asthma and GERD has been recognized for many years. Asthma symptoms; cough and chest discomfort may overlap with those of gastro esophageal reflux, making it difficult to distinguish between the two conditions. The study was designed to be for 3 months, with a monthly follow up visit to investigate the relation between asthma and acidic, non acidic GERD. Patients were divided to three groups; 1.Chang Life style (CLS) plus Omeprazole (G1) 2.Omeprazole (G2) 3.CLS (G3). GERD symptoms, Lung function (LF), asthma control test (ACT), and the asthma control questionnaires (ACQ) were measured for all patient at every visit. Fifty four asthmatic patients having the symptoms of GERD were enrolled in the study. Their mean (SD) age was 48.6 (12.6) years, 21 Patient started in G1, 21 Patient in the G2 and 12 patients in G3. From the initial results in table 1 it was clear that Omeprazole alone does not show the optimum improvement in the ACT. The results showed that the level of improvement in GERD symptoms was the same in G1&G3. In contrast 100% improvement in LF was seen in G1 while only 38% in G3, which may be due to the effect of the non acidic GERD.

Table 1. Level of improvement of LF, ACQ, ACT and GERD symptoms in visit 2

	LF	ACQ	ACT	GERD
G1	100%	78%	100%	100%
G2	66%	50%	50%	23%
G3	38%	50%	50%	100%

In conclusion, CLS can improve the GERD symptoms but it should be combined with the PPI in order to improve the asthma control.

P3994**Effects of pantoprazole on pulmonary function tests of chronic obstructive pulmonary disease patients, with and without gastro esophageal reflux**

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Introduction: Association between gastro esophageal reflux (GERD) and spirometric finding in chronic obstructive pulmonary disease (COPD) is subject of controversy. The aim of this investigation is to determine the effect of proton pump inhibitor (pantoprazole) on spirometric finding of COPD patient.

Material & method: In this clinical trial, 60 COPD patients were selected and according to questionnaire divide in two groups: with and without GERD (36 and 24 patient respectively). All patient treated with oral pantoprazole 40 mg daily for eight weeks. Spirometry before and after treatment was done. FEV1/FVC, FEV1, FVC, PEF were measured in two groups.

Result: Mean PEF in COPD patients with GERD before (55.4) and after pantoprazol had significant difference (55.4, 61.5 respectively) (p = 0.009) but mean FEV1/FVC, FEV1, FVC in both groups and PEF in patients without GERD had no significant difference.

Conclusion: This study showed in COPD patient with GERD, treatment with 40mg pantoprazole daily improve PEF but has no effect on other spirometric parameters.

P3995**The relationship between obesity and distal airways**

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Introduction: Obesity is a risk factor for asthma-like symptoms. Small airway involvement has been linked to difficulties in controlling asthma. Forced Vital Capacity (FVC) fall at PC20 has been suggested as a potent marker of distal airway abnormalities. Whether obesity is associated with increased distal airway involvement remains unknown.

Hypothesis: We hypothesized that FVC fall at PC20 during a methacholine challenge was increased in overweight and obese patients with asthma-like symptoms.

Methods: 298 consecutive adult women with asthma-like symptoms underwent a methacholine bronchial provocation test according to ATS-guidelines. PC20 methacholine and FVC fall at PC20 were computed for all subjects. Bronchial Hyper-Responsiveness (BHR) was considered when PC20 was $\leq 1600\mu\text{g}$. PC15 and FVC fall at PC15 were recorded in patients who did not achieve a 20% fall of Forced Expiratory Volume in 1 second (FEV1s).

Results: A logistic regression with age, smoking and Body Mass Index showed that only obesity (BMI ≥ 30) increased the risk of BHR with an odds-ratio of 4.2 (95 CI: 1.670–12.295) (p=0.0041). BMI had no impact on the relationship between FEV1s and FVC (p=0.2490). On the other hand, BMI influenced the percentage fall in FVC at the PC15 only in patients with PC20>1600 μg (normal 9 \pm 13%; overweight 10 \pm 16% and obese 15 \pm 32%, p=0.0073).

Conclusion: Obesity is a risk factor for BHR in women patients with asthma symptoms. FVC fall at PC20 is not affected by the BMI. Nonetheless, in obese women with asthma symptoms but negative methacholine challenge, we observed a potential involvement of distal airways measured by the FVC.

P3996**Treatment with inhaled corticosteroids (ICS) and long acting b2-agonists (LABA) combination in patients with COPD: Possible way of optimization**

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Respiratory muscles dysfunction in patients with COPD could affect the inhalation technique and be one of the causes of ICS and bronchodilator's inefficacy.

Aim of study: To evaluate efficacy of Budesonide/Formoterol combination in dry powder inhaler (Symbicort, Astra Zeneca) in patients with COPD (stage III) with signs of respiratory muscles dysfunction.

Study population and Methods: 20 patients with COPD III (17 men, mean age 58.9 \pm 6.3 yrs), who regularly treated by high doses of any ICS and bronchodilators no less than three month made the study sample. All patients were current smokers and had signs of respiratory muscles dysfunction (P_{imax} ≤ 60 kPa).

At baseline all patient withdrawn from their COPD therapy and were prescribed Budesonide/Formoterol combination 320/9 mcg BID.

Pulmonary function tests (FEV1, MMLV), P_{imax}, 6MWD and plasma C-reactive protein were evaluated before and 12 months after beginning of the study.

Results: Results are present in Table 1.

Index	Baseline	12 months after start of treatment
FEV1 (% of predicted)	47.5 \pm 10.4	52.6 \pm 11.8
MMVL (% of predicted)	51.1 \pm 7.9	71.6 \pm 6.2*
P _{imax} (% of predicted)	39.7 \pm 5.6	58.6 \pm 7.3*
6MWD, m	273.4 \pm 21.6	359.7 \pm 23.4*
C-reactive protein, mg/dl	24.0 \pm 3.8	9.9 \pm 4.2*

*p<0.05.

Conclusions: Long-term prescription of Budesonide/Formoterol combination in dry powder inhaler (Symbicort, Astra Zeneca) in COPD patients with signs of respiratory muscles dysfunction significantly increase their MMVL, exercises capacity and reduce respiratory muscles fatigue and systemic inflammation.

P3997**A comparative study to evaluate the effects of salmeterol/fluticasone and formoterol/budesonide combinations on lung functions and sleep quality in asthma**

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Introduction: Asthma is a prevalent chronic inflammatory disorder associated with dyspnoea, deterioration of lung functions and a negative impact on the quality of sleep. Combination treatment with a glucocorticoid and a bronchodilator is the mainstay of treatment.

Aims and objectives: To evaluate the effects of two commonly used combinations salmeterol/fluticasone and formoterol/budesonide on lung functions, dyspnoea and the quality of sleep in patients with moderately severe persistent asthma.

Methods: Sixty patients of moderate severe asthma were allocated to two different treatment groups i.e. salmeterol/fluticasone and formoterol/budesonide in a prospective, open, randomized and comparative study over a period of 6 weeks. The lung functions and Borgs dyspnoea scoring were done at the baseline and at the end of 3 and 6 weeks. Quality of sleep was assessed at the same time intervals by Pittsburgh Sleep Quality Index (PSQI) for quality of sleep and day time sleepiness by Epworth Sleep Scale (ESS).

Results: Salmeterol/fluticasone and formoterol/budesonide, caused a comparable and significant improvement in the lung functions (FEV1, FVC, FEV1/FVC and PEF). The two treatments had a highly significant and comparable improvement in dyspnoea. Quality of sleep as assessed by PSQI and ESS also improved significantly with both the combinations. However the salmeterol/fluticasone was relatively superior in improving quality of sleep.

Conclusions: Both the combinations were equivalent in improving lung functions & dyspnoea but salmeterol/fluticasone combination was superior with respect to sleep quality.

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P3998**ACCORD COPD I: Safety and tolerability of twice daily acclidinium bromide in COPD patients**

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Introduction: Acclidinium bromide is a long-acting muscarinic antagonist in development for COPD. Safety and tolerability of acclidinium 200 µg and 400 µg BID in moderate to severe COPD patients were assessed in this Phase III study.

Methods: In this 12-week, double-blind study, COPD patients were randomised to acclidinium 200 µg, 400 µg, or placebo BID (1:1:1). Safety was assessed via adverse events (AEs), clinical laboratory measures, vital signs, and electrocardiograms (ECGs).

Results: Baseline demographics were similar across treatment groups (N=561). The number (%) of patients with a treatment-emergent AE (TEAE) was comparable between acclidinium 400 µg, 200 µg, and placebo [85 (44.7), 93 (50.5), 97 (52.2), respectively]. COPD exacerbation was the most frequently reported TEAE in all groups (12.4%, placebo; 9.2%, 200 µg; 7.4%, 400 µg). Incidence of serious AEs was low (2.2%-4.3% for all groups). Incidence of potential anticholinergic AEs (eg, constipation and dry mouth) was low (n≤3) in both acclidinium groups and comparable to placebo. The most frequently reported AEs resulting in discontinuation were COPD exacerbation (n=7, placebo; n=4, 200 µg; n=1, 400 µg) and dyspnea (n=2 each, placebo and 400 µg). One patient in the acclidinium 400 µg group died due to metastatic lung cancer but this was not considered to be related to treatment. Changes from baseline in laboratory tests, vital signs, and ECGs, were similar across all groups.

Conclusions: Acclidinium 200 µg and 400 µg BID were safe and well tolerated throughout this 12-week study with a low incidence of systemic anticholinergic adverse events, similar to placebo. There were no differences in safety profiles between the two acclidinium doses.

P3999**Differences in adherence to inhaled steroid medication in COPD**

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Objective: To study whether COPD patients on medication combining an inhaled steroid with a long-acting bronchodilator show better therapy persistence than patients with inhaled steroids alone.

Methods: This study is part of a cohort study with 3 years of follow-up (COMIC study). In total 800 patients were included. Therapy adherence was recorded from patients' pharmacy records and was expressed as a percentage that was deemed good if it was 75-125%, sub-optimal between 50-75%, and poor below 50% or above 125%.

Results: In total 664 (83%) patients used inhaled steroids and 60.8% showed good compliance. We observed a significant difference in therapy adherence between the studied medications (p< 0.001). These differences were observed between Fluticasone and Budesonide (p=0.001), Budesonide and Salmeterol/Fluticasone (p<0.001), and Salmeterol/Fluticasone and Formoterol/Budesonide (p=0.002). Fluticasone had the highest percentage of patients with good adherence. For Formoterol/Budesonide, Budesonide and Salmeterol/Fluticasone the percentages of good adherence were almost similar, but Formoterol/Budesonide and Budesonide showed a higher percentage of patients with poor (>125%) adherence, while Salmeterol/Fluticasone had a higher percentage of patients with sub-optimal adherence.

Conclusions: This study showed that a significant proportion of patients with COPD is poorly adherent to inhaled corticosteroid therapy. Furthermore, adherence rates differed significantly between the studied inhaled steroids and the combinations of inhaled steroids and LABA. Contrary to our hypothesis, the adherence did not seem to be higher in the combined medications in comparison to the inhaled steroids alone, and in some cases it was even worse.

P4000**The Dutch hypothesis, implications for treatment of chronic obstructive pulmonary disease and asthma in a biomarker, monoclonal antibody world. Experience with IgE and omalizumab in a small pulmonary practice**

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In 1961, Orie and colleagues from the University of Groningen in the Netherlands hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis and emphysema, should be considered not as separate entities but as different expressions of one disease entity. In a pulmonary practice patients with a physician diagnosis of chronic obstructive pulmonary disease (COPD) had phys-

iological and biochemical evaluation as part of their routine workup. They were treated with omalizumab if they were symptomatic despite adequate conventional treatment and had an elevated IgE level. Patients with COPD (n=60) who were on treatment with omalizumab for at least 6 months were asked to fill out a questionnaire from which their symptom scores (1-4) and satisfaction scores (1-5) were extracted. There was statistically significant improvement in the amelioration of both symptoms and increase in satisfaction scores (p was less than 0.01) with treatment with omalizumab. This year being the 50th anniversary of the Dutch Hypothesis, it may be appropriate to revisit this issue. Patients with COPD may benefit from evaluation and treatment with monoclonal anti-IgE antibody therapy. Randomized placebo controlled, double blinded trials are needed to help further define the role of anti IgE therapy in patients with COPD. Subsequently, the broad use of biomarkers to evaluate need for monoclonal antibody therapy may need to be reconsidered. To the treating physician and the patient the treatment outcome is more relevant than the actual diagnosis.

P4001**The effect of L-arginine on ciliary function in primary ciliary dyskinesia (PCD)**

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The nitric oxide synthase substrate, L-Arginine (L-Arg), has been shown to stimulate ciliary beat frequency (CBF) in PCD [1], however it is unclear if this effect was universal to the common phenotypes of PCD or if it could correct the ciliary beat pattern.

Aims: To study the effect of L-Arg on the ciliary function in 3 different phenotypes of PCD.

Methods: Nasal brush biopsies were taken from 15 PCD patients (5 inner arm, 7 outer arm, and 3 transposition defects) and 3 controls. The strips of ciliated epithelium were subjected to medium 199 Control or 5mM L-Arg for 10min at 37°C. The cilia were visualised by a light microscope and recorded using a high speed video. The recordings were analysed in a blinded fashion and were replayed at reduced rate for determination of CBF and cilia tip distance travelled.

Results: L-Arg treatment significantly (p>0.05) increased the CBF (from 5.6±1 to 8.3±1.5Hz) and tip distance travelled by the cilia (from 0.35±0.09 to 0.52±1.2cm) in all 15 PCD patients studied. Individual phenotypes of PCD showed a variable response to L-Arg. CBF and tip distance travelled by the inner dynein arm defects were significantly (p>0.05) increased by L-Arg treatment (CBF from 6.3±1.2 to 9.6±1.1Hz; tip distance from 0.44±0.15 to 0.67±0.2cm). The CBF and tip distance of the cilia from the other defects were not statistically different.

Conclusion: L-Arg increased CBF and ciliary tip distance in PCD, an effect that was increased in those with inner dynein arm defects. The mechanism and physiological significance of the changes remain to be determined.

Reference:

[1] Loukides, S., et al. Effect of arginine on mucociliary function in PCD. *Lancet* 1998;352(9125):371-2.

P4002**Formoterol, but not indacaterol, induces transient hypoxemia in severe COPD**

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β₂-agonists are effective options in COPD. Mainly the short-acting compounds can rapidly induce a transient hypoxemia by affecting pulmonary vasculature. Most recent long-acting β₂-agonists (LABA) were poorly investigated from this point of view.

Aim: Aim was to measure and compare the hypoxemic effect of Formoterol (F) and Indacaterol (I) in moderate-to-severe COPD.

Methods: 24 ex-smoker patients (18m; mean age= 70.3y±6.1sd; range 51-76; mean FEV1/FVC = 52.2% pred. ±9.0sd; mean FEV1= 50.0±11.8ds) were studied after their written informed consent according to a double-blind, double-dummy, cross-over, randomized design. Active drugs were F 12mcg and I 300mcg, assumed in two different days, with a 36h-interval in between. Arterial blood was drawn in baseline; after 5', and 30' from F and I; FEV1 was measured at the same times. **Statistics:** Friedman's analysis of variance by ranks and Page's test for trend, and p<0.05 accepted.

Results: See Table 1 (means ± sd).

Table 1

	Baseline	5 min	30 min	
PaO ₂ (mmHg)				
F	66.7 (6.5)	62.8 (5.8)	62.3 (7.1)	p<0.04
I	67.1 (4.6)	66.4 (5.7)	65.2 (5.2)	
FEV1 (% pred)				
F	49.9 (11.8)	52.7 (10.5)	53.0 (11.2)	p=ns
I	49.6 (11.6)	52.7 (10.7)	54.4 (11.5)	

Discussion: Both F and I induced rapidly an equal (p=ns) and significant (p<0.001) bronchodilation. The trends for PaO₂ changes were significantly different with the

two drugs ($p < 0.04$): F induced a sudden, substantial hypoxemia lasting at least for 30', changes following I were negligible.

Conclusions: 1) the safety of I is emphasized; 2) the peculiar chemical structure of I and the fact that it behaves as a nearly full β_2 -adrenoceptor agonist likely contribute to explain its ineffectiveness in terms of β_2 -induced hypoxemia in COPD.

P4003

An audit on emergency oxygen administration and safety issues

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Background: British Thoracic Society (BTS) guidelines on Emergency Oxygen (O₂) in 2008 highlighted the importance of safe prescription and administration of O₂. We audited our practice focussing on the documentation, prescription and complications in a busy district general hospital in UK.

Methods: Audit was performed on patients admitted to the medical admission unit over a period of 3 months between Jan 2010 to Mar 2010. Patients who had O₂ were randomly selected and monitored from admission to discharge.

Results: 56 patients in total were studied.

46% had assessment for the risk of CO₂ retention before O₂ started.

Only 34% had documentation of target O₂ saturations.

Documentation of Device in 66%, Flow in 71% and Fio₂ in 32% of cases.

96% of drug charts had no prescription of O₂.

There is no documentation how long O₂ should be given in all the cases.

20 (36%) patients had inappropriate administration of O₂; No need for O₂-10, More O₂ than needed-9 and Less O₂ than needed-1.

3 patients developed Type 2 respiratory failure and needed Non-invasive ventilation. There were no mortalities.

Conclusions: We identified safety issues whilst administering Emergency O₂ and need to improve in our documentation, prescription on drug charts and administration.

Patients at risk of CO₂ retention would have arterial blood samples after starting O₂.

Drug charts were modified adding oxygen in 2 areas: Regular and PRN sections and also include device, flow, Fio₂, target saturations and how long to give O₂.

Flow charts on how to administer and adjust O₂ were placed in all the wards including medical admission units.

Repeated mandatory educational training on O₂ administration to all medical, nursing and allied health care professionals were started.

P4004

No difference observed in the risk of malignancy in patients exposed to omalizumab compared with controls

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Previous pooled data from the omalizumab clinical trial programme (Phase I-III clinical studies) showed a numerical imbalance in cancers arising in omalizumab recipients. The incidence of malignancies in the omalizumab group was similar to that expected in the general population but higher compared with control, raising a question over omalizumab's long-term safety. To fully address this potential safety concern, a further analysis was conducted using additional pooled data to examine malignancy in omalizumab-treated patients. We used data from 32 randomized, double-blind, placebo-controlled trials (RDBPCTs) to assess incidence of primary malignancy. 7432 patients (4254 omalizumab, 3178 placebo) were included. Total observation times censored at first malignancy were 3382 and 2473 patient-years for omalizumab- and placebo-treated patients, respectively, including treatment exposure durations of 2143.9 and 1689.1 patient-years, respectively. Malignancy rates and corresponding changes in rate ratios over time are shown in the Table. No specific cluster of neoplasm was identified.

Primary malignancies in RDBPCTs	2003	2006	2010
Omalizumab rate*	5.86 (9 / 1536)	4.21 (9 / 2136)	4.14 (14 / 3382)
Control rate*	3.56 (4 / 1124)	3.50 (6 / 1715)	4.45 (11 / 2473)
Rate ratio (95% CI)	1.65 (0.46, 7.31)	1.20 (0.43, 3.38)	0.93 (0.39, 2.27)

*Malignancy rates per 1000 patient-years calculated from number of malignancies/observation time in patient-years.

Results of this pooled analysis show a progressive reduction of the rate ratio to below unity in cancers arising in the omalizumab group compared with control in RDBPCTs, and suggest that a causal relationship between omalizumab therapy and cancer is unlikely.

P4005

The ATTAIN study: Safety and tolerability of acclidinium bromide in chronic obstructive pulmonary disease

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Introduction: Acclidinium bromide is a long-acting muscarinic antagonist in clinical development for chronic obstructive pulmonary disease (COPD).

Aims: To assess the safety and tolerability of acclidinium 200 μ g and 400 μ g twice-daily (BID) in patients with COPD.

Methods: This 24-week, double-blind, Phase III study (NCT01001494) randomised patients to receive acclidinium 200 μ g, 400 μ g or placebo BID (1:1:1). Adverse events (AEs), clinical laboratory measures, vital signs and electrocardiograms (ECGs) were assessed.

Results: Baseline demographics were similar across all groups (safety population, N=819). The incidence of treatment-emergent AEs (TEAEs) was similar for placebo, acclidinium 200 μ g and 400 μ g (57.1%, 54.5%, 53.5%, respectively). COPD exacerbation was the most frequently reported TEAE in all groups (placebo, 20.5%; 200 μ g, 15.9%; 400 μ g, 14.1%). TEAEs reported by $\geq 2\%$ of patients and with a higher incidence in the acclidinium groups were: headache, nasopharyngitis, diarrhoea, cough and toothache. The incidence of TEAEs leading to discontinuation was similar across the groups (3-4%); COPD exacerbation was the most frequent reason (placebo, n=5; 200 μ g, n=3; 400 μ g, n=4). The incidence of anticholinergic AEs (<2.5% for each group) and of general serious AEs (4.3-5.5%, all groups) was low in all treatment arms. Changes in laboratory tests, vital signs and ECGs were similar between groups.

Conclusions: Acclidinium 200 μ g and 400 μ g were well tolerated with an incidence of AEs similar to placebo. There were no differences in the safety profiles between the acclidinium doses.

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P4006

Clinical efficacy of once-daily mometasone furoate in children with persistent asthma switched from treatment with fluticasone propionate

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Background: Mometasone furoate (MF) delivered via dry powder inhaler is an inhaled corticosteroid (ICS) for the treatment of persistent asthma in children ≥ 4 years. MF 110 μ g once daily in the evening (QD PM; approved pediatric dose) and MF 110 μ g twice daily (BID) were compared with placebo (PBO) in children aged 4-11 years with persistent asthma previously treated with other ICSs at stable doses for ≥ 2 weeks before randomization. The primary efficacy variable was change from baseline in % predicted forced expiratory volume in 1 s (FEV₁) at endpoint; primary results for 296 randomized children were published previously.

Objective: Investigate the possible relationship between the primary endpoint and previous ICS use.

Methods: Two post hoc analyses were conducted: one to determine whether children previously using different ICSs responded differently to MF; another to compare the effects of MF vs PBO in the subgroup of children previously using fluticasone propionate (FP).

Results: In post hoc analysis, no significant difference was found in the response to MF in 296 children previously using different ICSs ($P=0.6372$). Most children (160; 54%) previously used FP 88-440 μ g/d (median, 176 μ g/d). Post hoc analysis of treatment effects in the FP subgroup determined that changes in % predicted FEV₁ with MF 110 μ g QD PM, MF 110 μ g BID, and PBO were 6.4%, 4.3%, and -4.2%, respectively. The difference between both doses of MF and PBO was significant ($P < 0.004$).

Conclusions: Previous ICS use did not affect the efficacy of MF in children, and MF 110 μ g QD PM significantly improved lung function compared with PBO in children switched from FP.

P4007

Fluticasone propionate/formoterol fumarate combination therapy has comparable efficacy to its individual components administered concurrently

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Background: A combination of fluticasone propionate and formoterol fumarate (FLUT/FORM; *flutiform*[®]) in a single aerosol inhaler has been developed. This study investigated the efficacy and safety of the combination compared to its individual components administered concurrently (FLUT+FORM).

Methods: Patients aged 12 years or over (N=210) with mild to moderate-severe persistent, reversible asthma were randomized in a 1:1 ratio to 12 weeks of twice daily treatment with one of two doses of FLUT/FORM or FLUT+FORM in an open-label, parallel group, multicentre study in Europe. Total daily doses were FLUT/FORM: 200/20 μ g or 500/20 μ g; FLUT+FORM: 200/24 μ g or 500/24 μ g. The primary objective was to show non-inferiority of FLUT/FORM compared to FLUT+FORM based on post-dose forced expiratory volume in 1 second (FEV₁) on Day 84.

Results: FLUT/FORM had comparable efficacy to FLUT+FORM in the treatment of asthma with mean FEV₁ 30 to 60 minutes post-dose on Day 84 of 2.6L in both groups (per protocol groups; least squares mean difference: -0.03 L; 95%CI: -0.148, 0.081; p=0.004). The lower limit of the 95% CI was above the pre-defined non-inferiority threshold of \geq -0.2L. Analysis of other pulmonary function tests, patient reported outcomes, rescue medication use, asthma exacerbations and quality of life questionnaires were also comparable. The safety profiles of the two study groups were similar overall.

Conclusions: Fluticasone/formoterol combination therapy has comparable efficacy to its individual components administered concurrently. The safety and tolerability profile of fluticasone/formoterol combination therapy is similar to that of its individual components.

P4008

Body mass index, disease control and airway inflammation in asthmatic patients

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Background: The association between overweight and asthma remains controversial.

Aim: To investigate the relationship between body mass index (BMI), disease control and airway inflammation in an asthmatic population.

Methods: We consecutively studied 408 patients (43 \pm 16 yr; 248 F). In all patients, BMI, spirometry, Asthma Control Test (ACT) and Fractional Exhaled Nitric Oxide (FeNO, ppb) were measured.

Results: 205 patients had a BMI > 25 kg/m² and, as compared to those with normal BMI, had lower values of FVC, FEV₁, FEV₁/FVC, FEF₂₅₋₇₅, FEF₇₅ and FEF₂₅₋₇₅ (p<0.05 for each comparison). The ratio between the number of patients with well controlled asthma (ACT \geq 20) and that of patients with poor controlled asthma (ACT < 20) was significantly lower in patients with increased BMI (106/99 vs 131/71; $\chi^2 = 7.227$, p<0.01). In patients with increased BMI, the odds ratio of uncontrolled asthma was 1.723 (95% CI = 1.157-2.566). No difference was observed in FeNO values between the two groups of patients.

Conclusions: Our results show that in an asthmatic population, the increase in BMI is associated with poor spirometry and worse disease control, but not with FeNO values.

P4009

How does obesity correlate with severe asthma?

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Introduction: 10% of asthmatics have refractory disease. Cluster analysis has identified that BMI is a factor in defining phenotypes of severe asthma [1]. Obesity antedates asthma diagnosis [2], suggesting that obesity has a pathophysiological role.

Last year we reported the outcome of 115 patients with severe, treatment refractory asthma (ATS, 2000). This study looks at data from 374 patients from 4 UK centres, collected as part of the National Registry for dedicated UK Difficult Asthma Services.

Methods: Patients were divided into three groups by BMI: 18.5 to 24.99, 25 to 29.99 (overweight), and \geq 30 (obese).

Results: The table below highlights demographic data, lung function, steroid use and bone density between groups.

Conclusion: Severe asthmatics are more likely to be female although this does not appear to correlate to BMI. Raised BMI is associated with more GORD, greater

use of PPI's, increased KCO, but a reduction in aspirin sensitivity, and appears to be protective against osteoporosis at the neck of femur.

References:

- [1] Moore W, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. AJCCM 2009 epub ahead of print.
- [2] Shore SA. Obesity and asthma: cause for concern. Current Opinion in Pharmacology 2006;6:230-236.

P4010

Effects on adrenal function of a new combination of fluticasone propionate/formoterol fumarate administered to asthmatic patients and healthy subjects

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Background: Corticosteroid treatment is known to affect adrenal function via suppression of the hypothalamic-pituitary-adrenal axis. This effect was assessed for a new asthma therapy combining the corticosteroid fluticasone (FLUT) with formoterol (FORM) in a single aerosol inhaler (FLUT/FORM; *flutiform*[®]).

Methods: Healthy subjects and patients with mild to severe asthma were treated for 4 to 12 weeks with FLUT/FORM (100/10 μ g, 250/10 μ g, or 500/20 μ g b.i.d.) in 3 randomised, parallel-group studies comparing FLUT/FORM with FLUT, FLUT+FORM from separate inhalers, or placebo. The endpoints were changes in urinary and serum cortisol levels from baseline to end of study.

Results: No significant differences were observed in mean urinary cortisol levels with FLUT/FORM 100/10 μ g (N=38; mean 21.51 μ g/24h; p=0.733) or FLUT/FORM 250/10 μ g (N=40; mean 24.01 μ g/24h; p=0.510) compared with placebo (N=39; mean 21.95 μ g/24h). In a study using FLUT/FORM 100/10 μ g or 250/10 μ g, patients had similar mean urinary cortisol levels at baseline and end of study (N=27; 5.1 vs 6.0nmol/L). The corresponding mean serum cortisol levels were 372.9 vs 412.6nmol/L (N=104). Healthy subjects given FLUT/FORM 500/20 μ g had a decrease in both urinary and serum cortisol levels at end of study but this was less than with FLUT 500 μ g+FORM 24 μ g (urinary: N=24; 13 to 7nmol/24h vs 14 to 4nmol/24h; serum: N=24; 399 to 272nmol/L vs 430 to 154nmol/L).

Conclusions: Fluticasone/formoterol 100/10 μ g or 250/10 μ g showed no significant changes in urinary or serum cortisol levels. Fluticasone/formoterol 500/20 μ g had some effect on adrenal function but less than FLUT+FORM given at the same nominal dose.

Abstract P4009 – Table 1. Obesity and severe asthma

BMI	No	Gender (female)	GORD	PPI use	Aspirin sensitivity	KCO %	Bone density T-score (neck of femur)
18.5 to 24.99	92 (25%)	70 (76%)	30 (33%), n=90	24 (26%), n=91	13 (14%), n=90	95.9, n=58	-1.0, n=31
25 to 29.99	117 (32%)	60 (51%)	45 (41%), n=111	27 (23%), n=115	13 (12%), n=113	102.1, n=74	-0.25, n=52
\geq 30	159 (43%)	101 (64%)	78 (50%), n=157; p=0.038	60 (38%), n=158; p=0.02	6 (4%), n=150; p=0.013	104.7, n=107; p=0.0068	-0.05, n=65; p=0.0013