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419. Recent advances in the treatment and pathogenesis of pulmonary diseases

E4263

Influence of thiotriazolol on phlegm cytogram of patients with community acquired pneumonia (CAP)

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Aim: To study influence of Thiotriazolol on phlegm cytogram of patients with CAP of the 3rd group.

Subjects and methods: 120 patients with CAP of the 3rd group were examined. 50 of them, treated by standard therapy (antibiotics, broncholitics) were a control group. The rest 70 patients formed a basic group and were treated by standard therapy in addition with Thiotriazolol which has anti-inflammation and detoxication effects, stabilize the membranes of mast cells. Local anti-inflammatory effects of Thiotriazolol was evaluating by modification of cell's structure of phlegm.

Results: Before the treatment in cytogram of phlegm of patients of control group we revealed neutrofills – 63,30±3,34%, alveolar macrophages – 3,50±0,36%, epitheliocytes 11,50±0,96%. In phlegm of patients of basic group we discovered – neutrofills – 65,40±2,81%, alveolar macrophages – 3,50±0,36%, epitheliocytes 11,50±0,96%. In patients with CAP of the 3rd group in both groups we observed modification of cytogram of phlegm at the 3rd day of treatment. In cytogram of phlegm of patients of control group we evaluated: neutrofills – 55,70±4,11%, macrophages – 6,90±0,63%, epitheliocytes 16,00±2,50%. In cytogram of phlegm of patients, which took additional Thiotriazolol, it was proved: neutrofills – 44,50±2,39%, macrophages – 12,00±0,70%, epitheliocytes 24,90±0,91%.

Conclusion: The cytogram of phlegm of patients taking Thiotriazolol improved reliably and quicker than in control group: at the 3rd day of treatment was revealed grater reduction of neutrofills and increase of alveolar macrophages and epitheliocytes (P<0,001). It had influence positively of course of disease and prevents the complications.

E4265

Lazolvan in reactions of free radical oxidation

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Mucolytic preparation lazolvan (L) is widely used in the treatment of various lung diseases. The efficacy of L may be due to its potential influence on the processes of free radical oxidation (FRO).

The objective was to study the effect of L on the processes of FRO: the production of active oxygen forms (AOF) and peroxide lipid oxidation (PLO).

Methods: The method of chemiluminescence (ChL) registration was used to study the effect of various doses of L (0,005 mg/ml, 0,01 mg/ml, 0,05 mg/ml) on the production of AOF in experimental models and in the whole blood of healthy subjects as well as the intensity of PLO in liposome suspension.

Results: L administered at a dose of 0,005 mg/ml reduced intensity of ChL in experimental model where AOF were generated by 5,6% ±0,1 and ChL of the whole blood by 14,0%±0,3 (p<0,05), and ChL of liposomes by 7,0%±0,2 (p<0,05). L administered at a dose of 0,01 mg/ml reduced ChL intensity in experimental model by 10,7%±0,2 (p<0,05), ChL intensity of the blood by 16,4%±0,3 (p<0,05), ChL of liposomes by 16,7%±0,3 (p<0,05). The dose of 0,5 mg/ml of L reduces ChL intensity in experimental model by 18,1%±0,4 (p<0,05), ChL of the blood by 27,8%±0,9 (p<0,05), ChL of liposomes by 32,0%±1,4 (p<0,05).

Conclusion: The study showed that L possesses dose-dependent antioxidant activity. This property has pathogenetic value in the treatment of lung diseases associated with enhancement of FRO processes.

E4266

Diagnosis of myocardiodystrophy due to drug cardiotoxicity in patients with bronchial asthma

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To determine blood level of troponin I and MB-fraction of creatine phosphokinase (CPMB) in patients with BA treated with β₂-agonists and inhaled corticosteroids, to estimate the severity of the drug cardiotoxicity and correct diagnosed cardiotoxicity with Cardonat (contains 100 mg of L-carnitine, 50 mg of Lysine, 50 mg of Cocarboxylase, 50 mg of pyridoxal-5-phosphate and 1 mg of Cobamide).

85 patients with BA (age 37±2.1) were questioned with a questionnaire developed by the department of clinicoepidemiological research with addition according to the International Consensus of BA diagnosis and treatment. CPMB and troponin I levels in the serum were measured with an immunoassay. To evaluate asthma patients for endogenous intoxication average molecules (AM) level in peripheral blood and leukocyte intoxication index (Garkavi index) were determined. Assessed cardiotoxicity was treated with cardiocytoprotector Cardonat "Sperko Ukraine", 1 capsula 3 times p/d during 1 month.

Troponin I and CPMB blood levels increased 2 times in 84.7% of patients. Evaluation of the same patients also showed endogenous intoxication – increased AM levels and high leukocyte intoxication. Treatment with Cardonat provided both cardiotoxicity and endogenous intoxication reduction. Previously increased troponin I level decreased by 23,4%, CPMB level by 7,8%, AM level by 25% and the leukocyte intoxication index by 14,3%.

The value of diagnosing drug cardiotoxicity in patients by measuring CPMB and troponin I levels in the serum was confirmed. Treatment with cardiocytoprotector Cardonat showed ability to reduce sings of cardiotoxicity in patient with BA.

E4267

Transepithelial potential changes of isolated tracheal wall after application of ambroxol, N-acetylcysteine and guaiaacol

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Introduction: The mechanical stimulation of airway wall causes cough reflex and also the reaction of epithelial hyperpolarization by changes in sodium reabsorption, chloride secretion and another ions transport processes.

Aims and objectives: The study was aimed to check the influence of expectorant and mukokinetics drugs on reaction of hyperpolarization.

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Methods: The studies were carried out on tracheal fragments from 70 rabbits (outbred stock animals). The modified Ussing method was applied to measure of electrophysiological parameters of epithelial tissue and to enabled **gentle mechanical stimulation of mucosal surface of trachea** by jet-flux from peristaltic pump.

Results: In 41% examined fragments of tracheal wall amiloride inhibited the reaction of hyperpolarization (bumetanide was without effect), in 11% bumetanide inhibited hyperpolarization (amiloride was without effect), and in 48% of tissues the application of both amiloride and bumetanide did not inhibited hyperpolarization after mechanical stimulation. In the presence of expectorant/mukokinetics drugs the course of reaction of hyperpolarization was modified: after application of ambroxol to $-0,67 \pm 0,21$ mV, after N-acetylcysteine to $-0,79 \pm 0,29$ mV and after guaiaicol to $-0,27 \pm 0,12$ mV in comparison with control value to $-1,03 \pm 0,23$ mV.

Conclusion: Ambroxol, N-acetylcysteine and guaiaicol modified the epithelial hyperpolarization after mechanical stimulation. It is supposed that reaction has an adaptive value as it influences the interaction between mucus molecules and surface of epithelial cells.

E4268

Effects of corticosteroids on mucosal tolerance and on the development of human T cell subsets

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Background: We have shown that systemic treatment with dexamethasone eliminated the generation of IL-10-producing TReg cells and thus inhibited mucosal tolerance.

Aims: We first applied corticosteroid substances other than dexamethasone and analyzed for their capacity to inhibit respiratory tolerance.

Second aim was to analyze whether the route of delivery of corticosteroids influences their effects on respiratory tolerance. We compared the effects of inhalative versus systemic applications of steroid substances.

Our third aim was to demonstrate the effects of corticosteroids on the development of human T cell subsets (Th1, Th2, TReg, Th17).

Methods: Respiratory tolerance was induced in mice.

Corticosteroids were applied systemically or by inhalation. Further, we established polarizing cell culture conditions to generate human Th1, Th2, TReg or Th17 cells *in vitro*. We analyzed the effects of corticosteroids on the development of T cell subsets.

Results: Systemic application of dexamethasone, prednisolone or methylprednisolone inhibited the development of T cell tolerance *in vivo*. In contrast, inhalative treatment with corticosteroids appeared to have no effect on the generation of TReg cells and mucosal tolerance. The results of the experiments regarding the generation of human T cell subsets are pending and will be presented during the conference.

Conclusions: It is a class effect of systemically applied corticosteroids to inhibit the development of TReg cells. In contrast, inhalative corticosteroids showed no effects on the development of mucosal tolerance *in vivo*. Effects of corticosteroids on the development of various human T cell subsets will be presented and discussed.

E4269

Angiopoietin-1 variant, COMP-Ang1 attenuates hydrogen peroxide-induced acute lung injury

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Reactive oxygen species (ROS) play a crucial role in acute lung injury. Tissue inflammation, the increased vascular permeability, and plasma exudation are cardinal features of acute lung injury. Angiopoietin-1 (Ang1) has potential therapeutic applications in preventing vascular leakage and also has beneficial effects in several inflammatory disorders. Recently developed COMP-Ang1 is more potent than native Ang1. However, there are no data on effects and related molecular mechanisms of COMP-Ang1 on ROS-induced acute lung injury. We used hydrogen peroxide (H₂O₂)-inhaled mice to evaluate the effect of COMP-Ang1 on pulmonary inflammation, bronchial hyper-responsiveness, and vascular leakage in acute lung injury. The results have revealed that VEGF expression, the levels of IL-4, tumor necrosis factor- α , IL-1 β , intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in lungs, the levels of hypoxia-inducible factor-1 α (HIF-1 α) and NF- κ B in nuclear protein extracts, phosphorylation of Akt, and vascular permeability were increased after inhalation of H₂O₂ and that the administration of COMP-Ang1 markedly reduced airway hyper-responsiveness, pulmonary inflammation, plasma extravasation, and the increases of cytokines, adhesion molecules, and VEGF in lungs treated with H₂O₂. We have also found that the activation of HIF-1 α and NF- κ B and the increase of PI3K activity in lung tissues after H₂O₂ inhalation were decreased by the administration of COMP-Ang1. These results suggest that COMP-Ang1 ameliorates ROS-induced acute lung injury through attenuating vascular leakage and modulating inflammatory mediators.

E4270

Effect of U-74389G and alpha-tocopherol on amiodarone-induced pulmonary fibrosis in rats

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Pneumotoxicity is an adverse effect of great concern in patients on amiodarone (AD) pharmacotherapy. This is primarily due to the potential for development of pneumonitis and pulmonary fibrosis, a condition for which there is no effective treatment and the prognosis is poor. We tested the potential effect of 21-aminosteroid U-74389G and α -tocopherol against AD-induced pulmonary toxicity in the rat model.

Methods: The study was carried out on 64 male Wistar rats weighing 220-250 g. The animals were divided into four treatment groups: (1) – controls; (2) – treated intratracheally with AD; (3) – treated with AD and 21-aminosteroid U-74389G; (4) – treated with AD and α -tocopherol. AD was instilled intratracheally on days 0 and 2 (6.25 mg/kg with a 3.125 mg/ml water solution). U-74389G was injected at a dose 15 mg/kg and α -tocopherol was injected at a dose 50 mg/kg on day 0, 1 and 2, intraperitoneally. Pulmonary fibrosis was assessed biochemically by measuring hydroxyproline (HP) content in lung homogenate (LH) and histopathologically on day 7 and 28 after AD administration.

Results: AD altered HP levels on day 7 and did result in significant (50%) increase on day 28 after treatment in comparison with controls. The content of HP in AD + U-74389G (0.68 \pm 0.08 mcg/ml LH) in AD + α -tocopherol (0.83 \pm 0.31 mcg/ml LH) groups were decreased compared to AD alone (1.07 \pm 0.17 mcg/ml LH) on day 28. Intratracheal AD resulted in increased histopathological damage on day 28, as indicated by thickening of interstitial spaces, and this damages were attenuated by both combinations.

Conclusions: The antioxidants U-74389G and α -tocopherol can substantially protect animals from amiodarone-induced pulmonary fibrosis.

E4271

Azithromycin increases chloride efflux from airway epithelial cells

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CFTR and multidrug resistance (MDR) proteins are members of the ATP-binding cassette superfamily. Up-regulation of MDR has previously been shown after macrolide treatment in animals. CFTR and MDR can complement each other, eliminate toxic products from the cell and possibly function as chloride (Cl⁻) channels. It was investigated whether the macrolide azithromycin can stimulate Cl⁻ efflux from airway epithelial cells. CF and non-CF human airway epithelial cell lines (CFBE and 16HBE) were treated with 0.4, 4, and 40 μ g/ml of azithromycin for four days. Using a fluorescent Cl⁻ indicator, N-(ethoxycarbonylmethyl)-6-methoxyquinolinium bromide (MQAE), Cl⁻ efflux was measured in the presence or absence of specific inhibitors of CFTR and alternative Cl⁻ channels. Azithromycin (4 and 40 μ g/ml) had a significant dose-dependent effect on Cl⁻ efflux from CFBE cells ($p < 0.01$), but the effect of 0.4 μ g/ml azithromycin was not significant. A significant inhibition of chloride efflux was observed after exposure of azithromycin-treated cells to the CFTR inhibitor-172. The inhibitor of alternative Cl⁻ channels, gadolinium, had no significant effect on Cl⁻ efflux. Azithromycin had no significant effect on Cl⁻ efflux from non-CF 16HBE cells. In conclusion, azithromycin increases Cl⁻ efflux from CFBE cells via the CFTR channel *in vitro*, which may be a partial explanation for the positive effects of this drug on CF-patients.

E4272

Does treatment of allergic rhinitis with intranasal steroids improve asthma control

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Introduction: Unified airway hypothesis suggests that treating co-morbid allergic rhinitis (AR) in asthmatic patients should improve asthma control. Evidence however is equivocal. This study aims to assess if AR treatment with intranasal steroids (INS) further improved asthma control.

Objectives: To determine in subjects with co-morbid AR-asthma, whether addition of INS to standard asthma care, improves asthma control and spirometric measurements, when compared to standard asthma treatment alone.

Methodology: Prospective, randomised, open study. After 4 weeks run-in period with ICS-LABA combination, 60 patients with asthma and AR were randomly assigned to 8 weeks of treatment with INS (standard doses of mometasone furoate-

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cases) or oral antihistamine (controls), while ICS-LABA treatment continued in both groups. AR and asthma symptoms were assessed by questionnaire, visual analogue scores (VAS) and spirometry, at baseline, after run-in period and after 8 weeks of treatment.

Results: 40 Cases (19F, 21M); 20 Controls (8F, 12M). Significant differences at baseline between cases and controls were abolished after run-in period. Cases further improved significantly both subjectively (VAS score) and objectively (FEV₁, PEF, FEF₂₅₋₇₅) as compared with controls who showed no further improvement.

Change in spirometric values

Parameters (% predicted)	Cases: mean (SD)	controls: mean (SD)	P value*
FEV ₁ change	13.68 (16.01)	5.17 (9.87)	0.03
PEF change	19.72 (14.90)	6.05 (12.84)	0.001
FEF ₂₅₋₇₅ change	19.44 (24.01)	-0.64 (11.63)	0.000

* Student's t Test

Conclusions: Asthma control improves significantly when INS are added to ICS-LABA combination in patients with combined AR and asthma.

E4273

Use of Bisoprolol: comparison of symptoms worsening in patients with asthma and COPD

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Aim: To evaluate the safety of Bisoprolol, and to compare the worsening symptoms, in patients with asthma and COPD.

Subjects and methods: We assessed 73 patients with moderate persistent asthma (MPA) and 71 patients with stage 2 of COPD (FEV₁ between 60-80%, aged 55-64 vs. 57-65). Both groups (MPA and COPD) had coronary heart disease (CAD). After catheterisation confirmed CAD all were on Bisoprolol therapy (5 mg/day). We compared deterioration of symptoms of bronchial conductivity (FEV₁ 60-80, asthmatics vs FEV₁ between 50-80 patients with COPD, at starting point). In Follow up period of 15 months, we re-evaluate both groups.

Result: The deterioration was confirmed in 38.5% (N^o28) asthma patients (FEV₁ < 60) vs. 12.6% (N^o 9) patients with COPD.

Conclusion: Although Bisoprolol is selective beta-blocker it's not completely safety for use in patient with asthma and COPD. There is statistically significant difference in deterioration of symptoms of bronchial conductivity in asthmatics as compared to patients with COPD (38.5% vs. 12.6% P < 0.05).

E4274

Long acting bronchodilation of Spiriva[®] handihaler in COPD patients, the influence of the inhalation flow rate (IFR)

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Introduction: Tiotropium is effective, once daily bronchodilator that reduces dyspnea and improves health status. Tiotropium dose emitted from a Handihaler[®] has indicated that there is a significant reduction when patients inhale at IFR between 28.3 and 20 Lmin⁻¹.

Aim of the study: Is to assess the effect of Spiriva[®] on COPD patients.

Method: At visit 1 Spirometry was done for the included patients, current medication was recorded, IFR through the handihaler was measured using the In Check Dial (Clement Clarke) and all completed the St. George's Respiratory Questionnaire (SGRQ). Spiriva[®] prescribed for each patient and all asked to return three weeks later.

Results: 17 Male COPD patients were included, their mean (SD) age were 72 (7.4) years ranged from 56 to 85 yrs. According to the BTS classification 5 of them were mild while the other 7 and 5 were moderate and severe respectively. Their IFR through the Handihaler was > 28 Lmin⁻¹. The mean (SD) FEV₁ in the 1st visit for the mild cases was 75% (13.2), for the moderate was 51.3% (6.2) and for the severe COPD was 36.4% (6.3) of the predicted values. There was a significant improvement (P<0.001) in the lung function and SGRQ in visit 2 compared to visit 1 in all COPD stages.

Discussion: The results of the study indicate that Tiotropium has consistently been shown to have significant improvement on Spirometry and quality of life in patients with COPD.

Conclusion: Spiriva produces superior bronchodilation, improvement in dyspnea and quality of life. These findings need to be evaluated in severe patients with IFR < 20 Lmin⁻¹ through the Handihaler.

E4275

The effect of levofloxacin on the production of active oxygen forms by blood cells

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Levofloxacin (LF) – a respiratory fluoroquinolone is used in the treatment of lung diseases. Apart from its high antimicrobial activity LF effectiveness may be explained by its potential to affect the production of active oxygen forms (AOF) by the inflammatory cells.

The objective was to study the LF effect on the production of AOF in in-vitro experiments.

Methods: The method of luminol-dependent chemiluminescence (ChL) registration was used to study the production of AOF in the whole blood of healthy subjects and the effect of LF on this process. The preparation was added into the whole blood at doses of 0,005 mg/ml, 0,01 mg/ml, 0,5 mg/ml.

Results: LF at a dose of 0,005 mg/ml decreased ChL intensity of blood by 10,6%±0,2 (p<0,05). Introduction of LF at a dose of 0,01 mg/ml reduced ChL intensity of blood by 25,7%±1,2 (p<0,05). The presence of 0,05 mg/ml of LF resulted in the reduction of ChL intensity of blood by 36,8%±2,1 (p<0,05).

Conclusion: The study has demonstrated that LF has a dose-dependent antioxidant activity. The potential of LF to suppress production of AOF underlies the mechanism of its anti-inflammatory effect.

E4276

Double blind randomised placebo controlled study of effect of inhalation of (72% O₂ and 28% helium) on perception of methacholine induced breathlessness in asthma

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Mixtures of helium and oxygen (Heliox) has been suggested as a treatment option in acute asthma, but support for this is limited. This study aimed to assess the efficacy of 72% helium/28% O₂ gas mixture (Heliox) on the perception of breathlessness induced by methacholine challenge with that of 72% nitrogen/28% O₂ (control). Twenty mild/moderate asthmatics (GINA guidelines), who showed at least a 20% fall in FEV₁ after methacholine challenge received either Heliox or control gas delivered via a face mask (at flow rate of 10 litre/min) in 2 visits 3 weeks apart in a double blind, randomised cross-over design. Change in the breathlessness score measured by visual analogue score (VAS) from the point when FEV₁ fell by 20% to 5 minutes after gas exposure was compared between groups as the primary end point. Secondary endpoints include change in VAS score (for tightness and wheeze), FEV₁, O₂ saturation, and impulse oscillometry (IOS).

There were no serious adverse events observed with either Heliox or control gases. The mean fall in FEV₁ after methacholine was 23.8% and 28.2% for the heliox and control gas days respectively. There was no significant difference in change in breathlessness (11.8 versus 9.3%), wheeze (14 versus 7.9%), tightness scores (11 versus 8.7%) or O₂ saturation following Heliox inhalation compared to control. We conclude that 5 minutes of Heliox inhalation did not alter significantly the perception of methacholine induced breathlessness in this cohort of mild/moderate asthmatics. Further study in severe asthma with extended period of gas exposure may be required to assess Heliox efficacy in acute asthma.

E4277

Cytokines status, endothelial function in patients with pulmonary diseases

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The aim of this study was to investigate possibilities of endothelial, immunological disorders correction by pentoxifylline in pts with pulmonary diseases.

Methods: 43 pts (17m, 26w) (16 COPD pts (age 60±2), 15 sarcoidosis pts (age 47±2), 12 idiopathic pulmonary fibrosis (IPF) pts (age 53±4) and 23 healthy volunteers were examined before and after 3 weeks of treatment. Pts were divided in to 2 groups. 23 Pts have been treated with basic course (β₂-agonist, anticholinergic, corticoids, O₂) and pentoxifylline 800mg/day (Gr1), 20 pts have received basic course only (Gr2). Pulmonary function tests, serum and exhaled breath condensate levels of IL-1RA, IL-8, TNFα, ultrasound detection of endothelial function, doppler-echoCG had been performed in all persons.

Results: In all COPD, IPF pts were found (p<0,01) pulmonary function, endothelial and haemodynamic disorders. After 3 weeks of treatment in Gr1 clinical status, endothelial function, immunological data were improved: in COPD, sarcoidosis, IPF pts was found increase of endothelium-dependent dilatation (on 111%, 87%, 90% accordantly, p<0,01), in COPD pts – increase of endothelium-independent dilatation (in response to nitroglycerine) (on 59%, p<0,01). In Gr1 was found decrease serum and exhaled breath condensate levels of IL8 (from 9,9±3,1; 11,6±1,9 to 3,6±0,3, p<0,05; 7,4±0,9pg/ml, p<0,05), TNFα (from 4,9±1,5; 5,8±1 to 1,8±0,1, p<0,05; 3,7±0,4pg/ml), increase of IL1RA (from

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786.9±134; 85±57 to 1140±118, p<0.05; 147±70pg/ml accordantly). In Gr2 significant changes were not found.

Conclusion: In pts with pulmonary diseases adding pentoxifylline to basic course leads to improvement of clinical status, endothelial function, immunological status.

E4278**Randomized double blind comparison of ciclesonide-formoterol combination inhaler and ciclesonide alone in persistent asthma**

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Background: The combination of an ICS and LABA is now accepted as a standard approach to treat patients with moderate to severe persistent asthma. Ciclesonide is a novel ICS with an improved safety profile and formoterol is a selective LABA.

Objective: To compare the efficacy and safety of a combination inhaler containing Ciclesonide and Formoterol with Ciclesonide alone in subjects with persistent asthma.

Methods: Subjects with FEV₁ 50% to 80% of predicted entered into a 1-4 weeks run-in period during which they received one inhalation of ciclesonide 80 mcg once daily in the evening and levalbutamol as rescue medication. Patients who remained symptomatic were randomized to receive one inhalation twice daily of either ciclesonide 80 mcg (C) or ciclesonide/formoterol 80/4.5 mcg (C+F), both by pMDI for 6 weeks in a randomized double blind double dummy fashion.

Results: Out of 169 patients enrolled, 160 completed the study. Mean morning peak expiratory flow rate (PEFR) increased significantly in the C+F group vs C [31.3 L/m (CI: 23.4, 39.2) vs. 11.3 L/m (CI:1.6, 21), p=0.001]. Evening PEFR also showed similar changes: 30.2 L/m (CI:22, 38.4) Vs 15.4 L/m (CI:6.4, 24.4). The differences were significant from week 1 onwards. There was a trend towards a greater improvement in FEV₁ in C+F group vs. C: 0.08 L Vs 0.03 L (p=0.06). Rescue medication use declined by 1.51 puffs in the C+F group vs. 0.92 puffs in the C group (p=0.052). Symptom scores showed no difference. Adverse events were similar in both groups.

Conclusion: Ciclesonide/formoterol combination inhaler is effective and well tolerated in patients with moderate to severe persistent asthma.

E4279**Effects of tiotropium on systemic inflammation and nutrition status**

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Background: Chronic obstructive pulmonary disease (COPD) is characterized by the progressive development of airflow limitation that is not fully reversible. There is increasing evidence that patients with COPD have extrapulmonary involvement including systemic inflammation and nutritional abnormalities. Tiotropium bromide improves lung function and quality of life in stable COPD. The purpose of this study is to determine the effects of tiotropium bromide on systemic inflammation and nutritional abnormalities in patients with stable COPD.

Methods: In this single-arm, open-label study, we recruited 25 patients with stable COPD. Patients were assigned to tiotropium bromide at 50 µg once a day for 2 months. Lung function test, SGRQ, inflammatory markers (serum hsCRP, TNF-α, IL-6), and nutrition markers (transferrin, retinol, prealbumin) were evaluated before and after tiotropium treatment.

Results: Lung function test (FEV1 and FVC) was significantly improved by tiotropium bromide. SGRQ scores were also increased after tiotropium treatment. However, there were no significant changes in serum hsCRP (2442.9 vs. 1793.8 ng/ml), TNF-α (2.51 vs. 2.61 pg/ml), or IL-6 (2.63 vs. 2.69 pg/ml) levels after tiotropium bromide use. None of nutritional markers (transferrin 251.6 vs. 248.3 mg/dl; retinol 4.45 vs. 4.61 mg/dl; prealbumin 26.1 vs. 26.7 mg/dl) was changed before and after treatment.

Conclusion: Although treatment with tiotropium improved lung function and QOL, it was not sufficient for improvement of systemic inflammation and nutrition status in patients with COPD.

E4280**CT densitometry for the assessment of AAT augmentation therapy: whole lung versus regional data**

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Rationale: Therapeutic effect of intravenous augmentation therapy with Prolastin[®] has been demonstrated in alpha-1 antitrypsin (AAT) deficient subjects using whole lung computed tomography (CT) densitometry. Emphysema is not uniformly distributed and therefore a treatment effect may be more evident using targeted sampling.

Objective: The EXAcerbations and CT scan as Lung Endpoints (EXACTLE) trial compared regional with whole lung CT densitometry for the assessment of augmentation therapy in AAT deficiency.

Methods: Patients with AAT deficiency (n = 77; three centres) were randomised to weekly infusions of 60 mg/kg human AAT (Prolastin[®]) or placebo (2% albumin) over 2 to 2.5 years. Densitometric progression was assessed using 15th percentile density (PD15) adjusted for lung volume using four different methods [1], and comparison made with targeted regional sampling from the apical, middle and basal thirds.

Results: A treatment effect was identified, which was more evident in the basal third (Table).

	Method of Adjustment			
	1	2	3	4
Estimated Treatment Difference, g/L				
Whole lung (P-value)	0.857 (0.068)	0.700 (0.059)	1.596 (0.084)	1.472 (0.049)
Basal (P-value)	1.043 (0.042)	0.897 (0.028)	1.843 (0.077)	1.722 (0.040)
Middle (P-value)	0.559 (0.328)	0.500 (0.274)	1.243 (0.265)	1.312 (0.155)
Apical (P-value)	0.472 (0.534)	0.279 (0.654)	0.672 (0.684)	0.581 (0.673)

Conclusion: A treatment effect of AAT augmentation was most sensitively detected in the basal third of the lung.

Reference:

1. Stockley, RA, et al. Proc Am Thorac Soc. 2008.

E4281**Lung deposition of inhaled radio-labelled human insulin**

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Aim: To determine the lung deposition of inhaled radio-labelled human insulin.

Methods: 11 healthy subjects were enrolled in the trial. Three subjects (control) inhaled human insulin spiked with Iodine-123 (¹²³I) and eight subjects (exposed) inhaled ¹²³I-labelled human insulin using the AERx[®] insulin Diabetes Management System (iDMS). Scintigraphic images of head/neck, thorax and abdomen were collected in the interval 0-24 hours post dosing. Images of the retained ¹²³I-labelled insulin in the inhaler device, used strips, exhalation filter and mouth washings were performed for mass balance calculations. To define the ventilated area of the lungs ^{81m}-Krypton gas was used.

Results: The device was set to emit 6 AERx units of insulin throughout the study, and the strips (10 AERx units) contained an average of 22.4 MBq of ¹²³I-labelled human insulin. The average deposition (inhaled dose) in exposed subjects was approximately 8.81 MBq, of these, 84.2% initially reached the lungs and 2.6% reached the trachea while the remaining 13.2% deposited in the oral cavity. Of the total loaded dose (nominal dose) 64.3% reached the lungs, 1.8% reached the trachea and 13.1% reached the oral cavity while the remaining 20.8% stayed in the inhaler device, strips or was exhaled again. The deposition and distribution of ¹²³I-labelled insulin in left versus right lung was similar to that of krypton.

Conclusion: Our results demonstrate a very high deposition of ¹²³I-labelled insulin in the lungs, a deposition which is primarily peripheral in the lungs with only very little deposited in the upper airways and oropharyngeal region.

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E4282**Evening administration of tiotropium during combination therapy reduces night-symptoms in COPD patients**

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Combination therapy showed additive effects in COPD on FEV1, hyperinflation,

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exertion dyspnoea and exercise endurance. An accurate timing of bronchodilation is essential to achieve the best control of airways.

Our study

aims: to determine which timing of therapy with formoterol (FOR) and tiotropium (TIO) (morning or evening) in moderate and severe COPD shows a greater functional improvement during 24h and a reduction of symptoms.

Methods: in a crossover study 80 patients with stable COPD received two 30days-treatments in random order. **TrA:** TIO 18µg(8AM) + FOR 12µg twicedaily; **TrB:** FOR 12µg twicedaily + TIO 18µg(8PM). Spirometries were performed during 24h on Day1 and 30, and a Transitional Dyspnoea Index (TDI) was assessed. A diary of use of salbutamol as-needed and symptoms (cough, night awakening) was utilized, recording separately for day-time and night-time. Gain of FEV1 (Δ FEV1) from baseline, dyspnoea, use of salbutamol, and symptoms were end-points.

Results: 68 patients completed the study. Daily functional improvement and dyspnoea index were essentially similar during TrA and TrB (Δ FEV1 in mL Day1 +135.8 and +119.1; Day30 +160.2 and +160.5; TDI +2.61, and +2.32 respectively). The mean of night-time puffs of salbutamol as needed and the night-symptoms (cough and night awakening) were significantly less during TrB (TrA: day 0.59 puffs/die, night 0.21; TrB: day 0.65, night 0.05*), (mean night-awakening TrA 2.3 and TrB 1.4*).*p<0.05

Conclusions: combination therapy with tiotropium in the evening, rather than in the morning, reduced night-symptoms and use of salbutamol. A rational timing for administration of the combination therapy can improve sleep quality in COPD.