Effects of smoking and oxidative stress on airway remodeling and phenotypic changes of the airway epithelium in asthma and COPD: strategies to restore the epithelial barrier, repair and steroid sensitivity

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON33504

Source
ToetsingOnline

Brief title
Effects of oxidative stress on epithelial cells and steroid-sensitivity

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Asthma, COPD, emphysema

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KNAW hoogleraarschap van Professor Postma,Astra Zeneca

Intervention

Keyword: asthma, COPD, Epithelial integrity, oxidative stress, smoking

Outcome measures

Primary outcome

- changes in epithelial integrity as measured with electrical cell impedance (ECIS) (during various conditions, i.e. with and without exposure to oxidative stress, with and without treatment with corticosteroids, with and without treatment with acetylcysteine, theophylline, heme oxygenase, carbon monoxide).

Secondary outcome

- production of pro-inflammatory cytokines during various conditions.

- markers of epithelial integrity (e.g. E-cadherin, caveolin-1) during various conditions.

- In biopsies the macroscopic quality of the bronchial epithelium will be assessed. In addition, we will investigate the expression of E-cadherin, caveolin-1 and heme-oxygenase.

Study description

Background summary

Asthma and COPD are chronic inflammatory airway diseases affecting millions of people worldwide. Inhaled corticosteroids (ICS) are by far the most effective

treatment with a broad anti-inflammatory spectrum. Nevertheless, most COPD patients and a proportion of severe asthma patients are corticosteroid-resistant (CR) and to fail to respond to ICS even when higher doses are given. These corticosteroid-resistant patients suffer from persistent symptoms and repeated asthma exacerbations. It has been suggested that smoking and oxidative stress may induce corticosteroid-resistance. The reactive oxygen species (ROS) responsible for oxidative stress can be generated exogenously (air pollutants, cigarette smoke) and endogenously by metabolic reactions. After inhaling air pollutants or cigarette smoke, the bronchial epithelium is exposed. Preliminary data from our own lab suggest that smoking and oxidative stress may decrease epithelial cell-cell contact formation. This results not only in a decreased barrier function, but also in an increased production of pro-inflammatory mediators.

Study objective

With this research project, we will investigate the effects of smoking and oxidative stress on epithelial barrier function in patients with asthma and COPD.

The most important research questions are:

1) Does exposure of cultured human epithelial cells to cigarette smoke or oxidative stress decrease cell-cell contact formation and reduce the level of caveolin-1?
2) Does exposure to cigarette smoke or oxidative stress render human cultured bronchial epithelial cells less sensitive to the positive effects of corticosteroids ?
3) Can the effects of smoking/oxidative stress on cultured human bronchial epithelial cells be counteracted by (combinations of) corticosteroids, *2-agonists, heme oxygenase-1, exposure to carbon monoxide, or vitamin D3? Is this associated with an increase in caveolin-1?
4) What are the effects of modulation of caveolin-1 on cell-cell contact formation?
5) Are there differences with respect to the above between patients with allergic or non-allergic asthma, COPD, or healthy subjects?
6) Are there differences between cultured epithelial cells derived from bronchial brushing and epithelial cells derived from nasal brushing?

Study design

This is an observational study. We will include a total of 60 well characterized (lung function, PC20 methacholine, skin prick test) patients with asthma and COPD. We will perform nasal and bronchial brushings. In addition, bronchial biopsies are taken to investigate the level of epithelial shedding and markers of epithelial integrity such as E-cadherin and caveolin-1. In

addition, we will investigate the expression of heme oxygenase 1.

Cultured epithelial cells will be stimulated with relevant inflammatory mediators (e.g. TNF-*., IL-13) and the production of pro-inflammatory mediators TARC, TSLP, IL-6, GM-CSF will be assessed in the presence and absence of budesonide. Next, oxidative stress will applied by maintaining subconfluent cells for 24 (or 48 hours) under 5% CO2/95% O2 which results in the production of ROS. This allows us to investigate the effects of oxidative stress on development corticosteroid resistance and the underlying mechanisms involved (i.e. effects on the level of NF-*B (both cytoplasma and nucleus), glucocorticoid receptor (GR)* and GR*, glucocorticoid responsive element (GRE), HDAC-2, and p38 MAPK). Finally, we will assess the effects of treatment aimed to protect against oxidative stress (e.g. N-acetylcysteine, upregulation of HO-1 (protoporphyrin, adenoviral constructs), CO, curcumin, and resveratrol). Finally, we will investigate the effects of treatment aimed to improve corticosteroid responsiveness (e.g. *2-agonists, theophylline).

Study burden and risks

This study is not associated with large risks. Possible adverse reactions may be:

- Blood collection may be painful and cause skin bruising.
- The provocation test with metahcholine may cause temporary dyspnea.
- The bronchoscopy may cause irritation of the airways and the bronchial biopsy may cause local bleeding.
- The nasal brush may cause irritation of the nasal mucosa and may cause local bleeding.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

inclusion criteria for patients with allergic asthma : ;* Age between 18 and 65 years.
* * 10 packyears, no smoking in the last year.
* The presence of allergy defined as at least one positive wheal/flare reaction (*2 mm relative to control) to a skin prick test with sixteen common aero-allergens).
* FEV1 > 80% predicted.
* PC20 methacholine or PC20 histamine < 8 mg/ml.;inclusion criteria for patients with COPD :
* Age between 45-75 years.
* * 10 packyears.
* FEV1 between 30% and 80% of predicted.

Exclusion criteria

*Any disease that, as judged by the Investigator, could have affected the outcome of this study.
*A respiratory tract infection within 4 weeks of the start of the study.
*A history of life-threatening asthma, defined as exacerbation of asthma or COPD that required intubation or was associated with hypercapnea.
*History of myocardial infarction or documented myocardial ischemia.
*Pregnancy, or the possibility of being pregnant (a pregnancy test will be performed in women of childbearing potential who do not use adequate anticonception as judged by the investigator).

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-07-2019
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT00849433
CCMO	NL26606.042.09