An early diagnosis of asthma in young children by using non-invasive biomarkers of oxidative stress/airway inflammation, and early lung function measurements

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This research proposal tests the hypothesis that an early asthma diagnosis is possible by using non-invasive biomarkers of oxidative stress/airway inflammation in exhaled air, venous blood and assessments of lung function (airway resistance by means...

Ethical review	Not approved
Status	Will not start
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON30167

Source
ToetsingOnline

Brief title
Early diagnosis of asthma in young children

Condition

- Respiratory tract infections

Synonym
asthma

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Ziekenhuis Maastricht
Source(s) of monetary or material Support: Astra Zeneca,Nederlands Astmafonds

Intervention

Keyword: asthma, early diagnosis, inflammatory biomarkers, transient wheezing

Outcome measures

Primary outcome

The primary outcome parameter in this study is the definite diagnosis of

asthma at the age of 6 years.

Morover, primary parameters are:

- Nitric oxide (NO) in exhaled breath

- Breathogram of volatile substances in expired air

- Exhaled breath condensate

- Lungfunction measurements of airway resistance

- markers in venous blood for: white blood cell count, differentiation, number

of eosinophils, total and specific IgE, cytokine profiles, the presence and

function of regulatory T-cells, markers of oxidative stress, gene expression of

markers of oxidative stress and inflammation

- Respiratory symptoms and quality of life

Secondary outcome

Secundary study parameters:

- asthma medication (dose, period) during the follow-up phase

- presence of other allergic diseases like eczema and/or allergic

rhinoconjunctivitis

- hospital admissions because of respiratory problems

Study description

Background summary

Asthma is a disease characterised by chronic airway inflammation. The prevalence of asthma in children in Western industrialised countries varies between 5-30%, and has increased in the past two decades. There are large problems with the diagnosis of asthma in young children. About 70% of children with recurrent asthma-like symptoms is symptom-free at 6 years and does not has asthma. The other 30% has asthma. Currently, an early and reliable diagnosis of asthma in young children is not possible with the conventional diagnostic measures. However, such a reliable diagnosis is important for the correct treatment of young children with respiratory symptoms. An effective therapy of asthma by means of anti-inflammatory treatment with inhaled corticosteroids is available. This treatment has a beneficial influence on airway inflammation, respiratory symptoms, asthma exacerbations, quality of life, lung function, and may reduce irreversible damage (*airway remodelling*) to the airways. It is also known that inhaled corticosteroids are not very effective in children with transient wheezing, and therefore treatment of these children is unnecessary, and leads to preventable costs and side-effects. Therefore, an early diagnosis will prevent undertreatment of true asthmatics and overtreatment of transient wheezers. This is of great importance for both infants and parents. In the past few years, relatively new lung function tests became available, and has been applied in young children. So far, measurements of oxidative stress/airway inflammation do not play a part in the diagnosis of asthma. It is probable that inflammatory biomarkers in exhaled air, and venous blood can reliably indicate an asthma diagnosis.

Study objective

This research proposal tests the hypothesis that an early asthma diagnosis is possible by using non-invasive biomarkers of oxidative stress/airway inflammation in exhaled air, venous blood and assessments of lung function (airway resistance by means of the interrupter technique).

Study design

A standardised questionnaire on respiratory symptoms (ISAAC) will be completed

in 1500 children aged 2-3 years in general practice (from the Registration Network of Family Practices of the University of Maastricht) and a birth cohort study (KOALA study). From the results of the ISAAC questionnaire, a prospective, matched, case control study is started of 200 children with recurrent respiratory symptoms (= cases) and 50 control subjects (=controls) with no or minor respiratory symptoms. At 6 years, a reliable, definite diagnosis of asthma is made (primary outcome measure) on basis of lung function assessments (maximal expiratory flow-volume curves before and after a bronchodilator, bronchial hyperresponsiveness) and current respiratory symptoms. At 2-3 years, repeated measurements of important predictors are performed:1) nitrogen monoxide (NO) in exhaled air; 2) a profile of inflammatory biomarkers in exhaled air by means of gas chromatography time-of-flight mass spectrometer (GC-TOF-MS); 3) airway resistance before and after a bronchodilator by means of the interrupter technique (Rint); 4) the improvement in inflammatory biomarkers and airway resistance during a 2-month treatment with an inhaled corticosteroid.
At the start (2- 3 years) and at the end (6 years) of the study 8 ml venous blood, a swab and a faeces sample will be sampled for 1) white blood cell count, differentiation, number of eosinophils; 2) total and specific IgE; 3) cytokine profiles; 4) the presence and function of regulatory T-cells; 5) markers of oxidative stress; 6) gene expression of markers of oxidative stress and inflammation; 7) polymorfism of relevant genes; 9) infection serology

Intervention

A trial with inhaled corticosteroids is part of the diagnosis phase of this study. Children in the experimental group will enter a controlled crossover trial with inhaled corticosteroids. This trial consists of a treatment period of 2 month with inhaled corticosteroid therapy (beclomethasone 2 times 100 microgram a day via the Airochamber ®), and 2-month period with placebo. Half the children start with inhaled corticosteroids, half start with placebo. All other anti-inflammatory medication will be stopped 4 weeks before the trial.

Study burden and risks

This research will last three to four years (dependent of the age of the child at entry). In the first year we will investigate the effect of a 2 month treatment with inhaled corticosteroids on lung function and inflammatory biomarkers in exhaled air. Measurements will take place at the start of the study, after 2 months and after 4 months. In the second and third year, measurements will take place once a year. At 6 years, a reliable, definite diagnosis of asthma is made.

Each visit at the hospital contains of 5 measurements:
1. A questionnaire will be taken to assess e.g. medication, respiratory symptoms
2. NO in exhaled air will be measured according to the standards of the ERS/ATS

. Exhaled air is collected via a face mask, covering the mouth, which is connected to a non-rebreathing valve that allows inspiration of NO-free air from a NO-inert reservoir to avoid contamination by ambient NO.
3. Exhaled breath condensate will be collected during tidal breathing, in a cooled tube for 10 minutes while children are wearing a nose-clib. During this test children can watch cartoons.
4. During tidal breathing, expired air will be collected in a 3-litre inert bag by means of a 2-way valve system.
5. Measurements of airway resistance will be performed by means of a simple lungfunction measurement.

At the start (2- 3 years) and at the end (6 years) of the study 8 ml venous blood, a swab will be sampled. A faeces sample will be collected

Contacts

Public
Academisch Ziekenhuis Maastricht

Postbus 5800
6202 AZ Maastricht
Nederland
Scientific
Academisch Ziekenhuis Maastricht

Postbus 5800
6202 AZ Maastricht
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Two groups are included:
- Children aged 2-3 years, with recurrent respiratory symptoms suggestive of astma;
- Children aged 2-3 years, with no or minor respiratory symptoms

Exclusion criteria

mental retardation, cardiac abnormalities, congenital anomalies, other respiratory diseases, chronic inflammatory diseases (e.g. Morbus Crohn, rheumatoid arthritis), inability to perform the exhaled air and lungfunction procedures properly

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	250
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Qvar Extrafine Aerosol 100 inhaler
Generic name:	beclomethasone dipropionate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-02-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	27-03-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2006-006736-22-NL
CCMO	NL11754.000.06