Assessment of inflammatory response of bronchial cells to gastric juice from hospitalized infants on and off proton pump inhibitor (PPI) therapy, PICU admitted children and long term users (0-18 years) of PPIs and controls off PPI

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Quantify inflammatory response (through IL-8 production) of bronchial (both commercial available cells and cultivated brushed infant cells) when exposing these to gastric juice from: hospitalized Infants, before and during PPI treatment and age...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal motility and defaecation conditions
Study type	Observational non invasive

Summary

ID

NL-OMON39158

Source
ToetsingOnline

Brief title
Bronchial inflammation to gastric juice from children on and off PPI

Condition

- Gastrointestinal motility and defaecation conditions
- Respiratory tract infections

Synonym
gastroesophageal reflux/heartburn - microaspiration induced respiratory tract infections/airway infections due to reflux in airway

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: bronchial cells, gastric juice, inflammatory reaction, protom pump inhibitor

Outcome measures

Primary outcome

* IL-8 production in two cell cultures (cultivated bronchial and child*s

obtained bronchial cell cultures) exposed to gastric juice from three patients

groups (hospitalized infants, PICU admitted children and long term PPI users.

* Determine relation between IL8 production of bronchial cells and

endotoxine/bile acid/pepsin/acidity levels in GJ from patients in all study

groups.

Secondary outcome

* Determine the composure (pH, concentrations of bile acid, pepsin and

endotoxine) of GJ in:

- Hospitalized infants,on and off PPI, before and during PPI treatment, before

and after feed.

- children admitted to the pediatric intensive care unit (PICU) before and

during PPI treatment.

- Children who have received and currently receive PPI treatment for at least

six weeks.

* Determine whether there is a difference in inflammatory reaction of bronchial

cells and GJ composure between breast milk fed and formula fed hospitalized

infants

* Measuring cytotoxic effect of GJ solutions on all cell cultures

Study description

Background summary

Gastro esophageal reflux (GER) is the passive movement of gastric contents into the esophagus. This is present in children in all age groups. Only when GER causes symptoms and complications it is referred to as GER disease (GERD). These symptoms may include: regurgitation, heartburn and unexplained crying. Extra esophageal symptoms and complications may include respiratory symptoms, such as chronic cough, apnea, wheezing, pulmonary fibrosis and pneumonia.
It has now become well accepted that not only acid, but also weakly acid and alkaline GER can cause significant symptoms and complaints of GERD and micro-aspiration of gastric contents is one putative mechanism behind the respiratory symptoms associated with GER. Micro-aspiration may cause an inflammatory response, which can ultimately lead to clinically relevant bronchitis and/or pneumonia. It is commonly thought that gastric contents are increasingly deleterious to bronchial tissue with increasing acidity and especially when pH drops below 4. However, recent evidence in animals and in adults, show that weakly acid and alkaline aspirated reflux might be able to provoke a significant greater inflammatory response compared to acid GER. This suggests that the acidity of gastric contents, presumably by its antibacterial qualities, could in fact play a role in the prevention of bronchial damage resulting from micro-aspiration following GER.
Proton pump inhibitors (PPI*s), a therapy focused on reducing the acidity, but not the number of GER episodes, are more and more used to treat GERD and prevent GER related respiratory symptoms in infants and children with increased risk of aspiration and/or the suspicion of impaired pulmonary clearance mechanisms. This is striking given the evidence available. Five out of five randomized controlled placebo controlled trials show no clinical effect of PPI treatment on GERD symptoms in infants and children. Moreover, PPIs might not be as safe as previously presumed. Studies report a number of adverse events such as gastric bacterial overgrowth of the upper gastrointestinal tract. With regards to respiratory adverse events, the following are described in literature in children and adults: community-acquired pneumonia an increase of respiratory tract infections in critically ill children and hospital acquired pneumonias. All of the above are attributed to the acid suppressing ability of PPIs.
The possible causal relationship between PPI use and respiratory tract

infections would be especially relevant for hospitalized infants, in whom an increase in the prescription of PPI is seen to treat and prevent respiratory symptoms which are clinically expected to be GER related (e.g. apnea), and in ventilated PICU admitted children, who receive PPI on a prophylactic base. Currently, it is unclear how gastric juice from hospitalized infants, PICU admitted children and children on long term PPI treatment influences inflammatory responses in bronchial epithelium.

Study objective

Quantify inflammatory response (through IL-8 production) of bronchial (both commercial available cells and cultivated brushed infant cells) when exposing these to gastric juice from: hospitalized Infants, before and during PPI treatment and age matched controls who do not receive PPI therapy, mechanically ventilated infants and children admitted to the pediatric intensive care unit (PICU) before and during PPI treatment and children who have received and currently receive PPI treatment for at least six weeks and controls not recieving anti-reflux treatment.

Study design

Prospective, observational, laboratory study.

Study burden and risks

With regards to gastric juice collection, two samples will be taken from patients admitted at the PICU wards and one from children who are on long term PPI treatment. In hospitalized infants, both GERD patients and controls, gastric juice samples will be taken 4 times: prior and after feeding, both prior and after start of PPI therapy. This is to analyse the effect of feeding on the composition of the gastric juice and the possible effects on the inflammatory response of bronchial cells. All samples will be taken through a catheter which is already in place and should therefore cause no additional discomfort or risk. One exception is the group of patients with long term PPI use. If these patients are not routinely fed through a nasogastric tube, the gastric juice will be taken during a routine pH or pH-impedance investigation A combined catheter will be used for this purpose and although the diameter of this catheter is slightly larger than that of the pH or pH-impedance catheter used for clinical purposes (6F compared to 4F), in our experience this procedure is well tolerated and should cause no or minor additional discomfort. No side effects are to be expected. In control patients, we will only collect gastric juice through an already existing nasogastric tube or PEG tube.
Also with regards to collecting primary bronchial cells through a blind brush procedure, which we will perform in 3 patients, minimal additional side effects are expected, since infants or children are intubated for either a surgical procedure or a broncho-alveolar lavage (BAL) procedure they need to undergo for

other medical reasons besides respiratory tract infections. No side effects of the brush procedure are foreseen.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Group 1 - Hospitalized infants
- Informed consent signed by care-givers
- Age ><=34 weeks GA to 6 months
- Admitted for reasons other than structural gastrointestinal disorders and where no suspicion of such an abnormality exist
- Tube fed
- Appointed to be treated with PPIs or no signs of GER related symptoms or aspiration risk

and thus unlikely to receive PPI in the near future.;Group 2 - PICU admitted children
- Informed consent signed by care-givers or patient if aged *12 years
- Age ><=34 weeks GA to 18 years
- Admitted for reasons other than structural gastrointestinal disorders and where no suspicion of such an abnormality exist
- Tube fed
- Mechanically ventilated
- Appointed to be treated with PPIs ;Group 3 * outpatient clinic children
- Informed consent signed by care-givers or patient if aged *12 years
- Age ><=34 weeks GA to 18 years
- who have received and currently receive PPI treatment for at least six weeks because of suspected GERD or NO anti-relfux therapy
- Appointed for intraesophageal evaluation of PPI treatment (eg. pHmetry, endoscopy, manometry) or having a permanent nasogastric/PEG tube

Exclusion criteria

- > 6 months (Group 1)
- Prematurity < 34 weeks GA at birth
- Previous gastro-intestinal (GI) surgery
- Structural GI abnormalities (exception group 3)
- Infectious gastro-enteritis
- Use of medications other than PPIs possibly influencing gastric conditions and/or GI motility
- Syndromes (exception group 3)

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	11-01-2013
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	12-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL39911.018.12