Response of sigmoïd epithelium to secretory stimuli in adults with constipation

Published: 13-01-2009
Last updated: 10-05-2024

To investigate a) the functional role of chloride secretion in constipated adults (Ussing chamber studies) and b) inventory possible aberrancies in in situ ClC-2/ CFTR expression levels by immuno-histochemistry staining techniques.

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

Summary

ID

NL-OMON31445

Source
ToetsingOnline

Brief title
Response of sigmoid epithelium to secretagogues

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
constipation, obstipation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: adults, constipation, secretion, sigmoid

Outcome measures

Primary outcome

Primary:

-Response of sigmoid tissue to secretagogues

Secondary outcome

Secondary:

- Baseline current

- Baseline potential difference

- CLC2 and CFTR expression in the mucosa of the sigmoid

Study description

Background summary

Approximately 12-27% of the population may suffer from functional constipation which seems to further increase with age. It is recognized by infrequent, hard stools, incomplete evacuation of stools and the involuntary loss of faeces in the underwear. It is a debilitating condition that is often associated with abdominal pain. To date however, treatment modalities are mainly based on empiricism and have little evidence of long-term efficacy. This is mainly due to the lack of knowledge on the pathophysiology which is most likely multifactorial and can result from behavioural factors, motility abnormalities or disturbances in fluid and / or electrolyte balance.
With respect to possible disturbances in fluid and / or electrolyte balance it should be noted that secretion of water and electrolytes by the gastrointestinal tract are central to its physiological functions. Factors that increase net water absorption (as opposed to secretion) will lead to harder stools and possibly constipation. The predominant electrolyte that drives intestinal fluid secretion is chloride, and its secretion is mediated by chloride channels in the apical membrane of the enterocyte. The importance of intestinal chloride secretion is emphasized by the congenital disorder cystic fibrosis that is accompanied by severe intestinal obstruction. In cystic

fibrosis constipation is caused by a mutation in one of the two Chloride channels that is important for intestinal chloride secretion, namely the cystic fibrosis transmembrane conductance regulator (CFTR). The other chloride channel that may be involved in non-cystic-fibrosis-related constipation is the eneterocyte-expressed ClC-2 channel located at the tight junction of the apical membrane.
The possible relevance of the ClC-2 ion-channel became apparent from preliminary studies on the chloride-channel activating compound Lubiprostone (SPI-0211). Its use showed a statistically significant increase in bowel movement frequency in constipated adults; from a range of 2.8*3.5 bowel movements/week in the placebo group to a range of 5.1*5.7 in the SPI-0211 treated group ($P < .002$). The main drug-associated side effect was nausea, but only a few patients withdrew because of this and no patients developed dehydrating diarrhoea. At this moment already 4 studies have been performed in constipated adults using this compound with positive results increasing frequency of bowel movements or accelerating colonic transit time. In a recent investigation, a human enterocyte cell line as well as ClC-2 and CFTR transfected human embryonic kidney cells were used to investigate the possible mechanism of action of SPI-0211. It was shown that the most probable target of this drug is not CFTR but the ClC-2 channel instead. However, only very few studies on the functional role of ClC-2 exist and functional investigations on intact human tissues have never been performed. Furthermore, there is a complete lack of publications on in situ expression levels of these chloride-channels in intestinal tissue of patients suffering from functional constipation.

Study objective

To investigate a) the functional role of chloride secretion in constipated adults (Ussing chamber studies) and b) inventory possible aberrancies in in situ ClC-2/ CFTR expression levels by immuno-histochemistry staining techniques.

Study design

Experiments:

Ussing Chambers
Functional ex vivo investigations on electrolyte transport can be performed in miniaturized Ussing chambers; forcepal endoscopic biopsies are mounted between the chamber halves where buffers circulate separately on the luminal and serosal sides. The spontaneous potential difference generated by the tissue is negated by injecting a current, known as the short-circuit current (Isc). Pharmacological agents added to either side of the chamber may alter active ion transport, which is shown by a change in Isc. A change of current indicates a change in chloride secretion.

In situ immunofluorescence investigations
The expression patterns of ClC-2 and CFTR in rectal mucosa of adults with functional constipation will be compared with controls. For this staining we will use the same biopsy that is present in the Ussing chamber. After completing the Ussing chamber experiments one biopsy will be used for immunohistochemistry staining.

Study burden and risks

The burden is that patients will undergo a sigmoidoscopy. This means that patients undergo such a procedure lasting for a total of 10 minutes.
The only benefit for those patients is that when we find a disturbed chloride secretion in those suffering from constipation, we will have a grounded reason for using Lubiprostone in our clinic in the future.

Case reports of perforation after sigmoidoscopy are described. However this risk is not high, approximately 0.5 pro mille.

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

- Patients with constipation defined by the Rome II criteria. At least 12 weeks of 2 or more of:
1. straining 1/4 defecations
2. Lumpy/ hard stools in 1/4 defecations
3. sensations of incomplete evacuation in 1/4 defecations;
4. sensation of anorectal obstruction/ blockade in 1/4 defecations;
5. manual maneuvres to facilitate >1/4 defecations
6. < 3 defecations/ week
Loose stools are not present, and there are insufficient data for IBS
- Controls: patients without constipation.

Exclusion criteria

- Administration of oral laxatives 2 days prior to the sigmoidoscopy;
- Administration of oral drugs affecting the motility of the intestine 2 days prior to the sigmoidoscopy;
- Malignancy of the gasto-intestinal tract and any other tract;
- Patients with metabolic disease (hypothyreoidia), inflammatory bowel disease, gastrintestinal surgery or congenital disorders;
- Patients with diarrhoea.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2007
Enrollment:	74
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
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	NL17967.018.07