Novel therapies for secretory diarrhea

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This study aims to assess the efficacy and potency of newly developed small molecule inhibitors of the GC-C signaling pathway and of the CFTR chloride channel in native human intestinal tissue.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal infections
Study type	Observational invasive

Summary

ID

NL-OMON39183

Source
ToetsingOnline

Brief title
Novel therapies for SD

Condition

- Gastrointestinal infections
- Bacterial infectious disorders

Synonym
ETEC infection, Traveler's diarrhea

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Institute for OneWorld Health;iOWH (NGO)

Intervention

Keyword: ETEC, guanylyl cyclases, heat-stable toxin, secretory diarrhea

Outcome measures

Primary outcome

The effect of 6 GC-C signaling blockers and of 4 CFTR inhibitors on the

pro-secretory response of human colon, assessed by ICM.

Secondary outcome

The effect of 6 GC-C signaling blockers on GC-C-independent intestinal solute

transport, assessed by ICM (off-target effects).

Study description

Background summary

Hyperactivation of the enzyme guanylyl cyclase C (GC-C) followed by excessive production of the signaling molecule cyclic GMP in the intestinal epithelium plays a central role in the disease mechanism of secretory diarrhea (SD) and, possibly, the irritable bowel syndrome (IBS-d). Newly developed inhibitors of GC-C signaling, shown to exert an anti-secretory and pro-absorptive effect on salt-and water transport in cultured enterocytes and in animal models, may therefore be used to treat SD. Activation of GC-C and of the enzyme adenylyl cyclase (AC) both result in the opening of CFTR, the major if not sole apical chloride channel in intestinal epithelium, encoded by the cystic fibrosis gene. Pharmacological inhibitors of CFTR are therefore expected to inhibit both GC-C and AC-mediated SD, including cholera, but such an inhibition has not yet been demonstrated convincingly in human intestine at the pre-clinical stage.

Study objective

This study aims to assess the efficacy and potency of newly developed small molecule inhibitors of the GC-C signaling pathway and of the CFTR chloride channel in native human intestinal tissue.

Study design

Rectal biopsies will be obtained from healthy volunteers. The effect of the

inhibitor compounds on the GC-C-and AC-mediated fluid secretory response of the intestinal mucosa will be studied ex vivo.
The test compounds have been selected on the basis of efficacy and potency in cell models of GC-C- and AC- mediated pro-secretory signaling. In view of subsequent structure-activity analysis, chemical diversity was also considered.
The ex vivo testing is performed by the intestinal current measurement (ICM) technique in micro-Ussing chambers. These experiments will show whether the GC-C- and CFTR-antagonistic action of our current selection of compounds, established in cell and animal models, is retained in native human intestine. Thus, they will also affirm, or refute, the validity of our preceding selection procedure, and allow structure-activity analysis to aid further development of novel anti-diarrheal drugs.

Intervention

Biopsies will be sampled from the rectum with a suction biopsy device.

Study burden and risks

The procedure to obtain rectal biopsies can be completed within 15 minutes. Including anamnesis, the whole procedure will take about 30 min. Tissue sampling is virtually painless, although accompanied sporadically with the loss of minute quantities of blood. The procedure is regularly performed for screening and research purposes in the context of Hirschsprung*s disease and cystic fibrosis. From this practice, it can be deduced that the risk of serious adverse effects is negligible.
No benefits are associated with participation.

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

Must be 18-55 years old.
Enrollment by informed written consent

Exclusion criteria

Liver conditions; signs of portal hypertension
Coagulation disorders or use of anti-coagulants
(Chronic) constipation. (As this may indicate aberrant intestinal ion and fluid transport.)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting

Start date (anticipated):	05-09-2013
Enrollment:	32
Type:	Actual

Ethics review

Approved WMO Date:	16-04-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL40609.078.12