Characterization Of Resistance Against Live-attenuated diarrhoeagenic E. coli

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Primary Objective: In the CORAL study we want to determine whether increasing the inoculation dose of diarrhoeagenic E. coli to 5*10^10 CFU and addition of a second challenge 1*10^10 CFU will result in an increased effect-size and duration of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal infections
Study type	Interventional

Summary

ID

NL-OMON42735

Source
ToetsingOnline

Brief title
CORAL

Condition

- Gastrointestinal infections
- Bacterial infectious disorders

Synonym
Gastroenteritis, traveller' s diarrhea

Research involving
Human

Sponsors and support

Primary sponsor: NIZO food research
Source(s) of monetary or material Support: Stichting Kernhem;Ede;The Netherlands

Intervention

Keyword: Enterotoxigenic E. coli, Gut infections, Traveller's diarrhea

Outcome measures

Primary outcome

Percentage of faecal dry weight (% determined by freeze-drying)

Secondary outcome

• Total faecal wet weight (faecal weight in g/day)

• Time to first diarrhoeal stool (reported by the subjects in the online diary)

• Stool consistency (Bristol Stool Scale reported by the subjects in the online diary)

• Number of stools with Bristol Stool Scale (Bristol Stool Scale reported by the subjects in the online diary)

• Stool frequency (Stools per day reported by the subjects in the online diary)

• Incidence and duration of WHO-defined diarrhoea (Calculated from the Bristol Stool Scale and the Stool frequency reported by the subjects in the online diary)

• Incidence, duration and severity of Gastro-intestinal symptoms (Gastro-intestinal Symptom Rating Scale reported by the subjects in the online diary)

Study description

Background summary

The WHO reported in 2007 that in industrialized countries, the percentage of the population suffering from food-borne diseases each year is up to 30%. This

is probably an underestimation, since recent data from a Dutch study indicate that the incidence of infectious intestinal disease is 964 per 1000 person years.
Travelers* diarrhoea is the most common health impairment in persons visiting developing countries, affecting up to 50-90% of travelers in high risk areas. Enterotoxigenic Escherichia coli (ETEC) the leading bacterial cause of travelers* diarrhoea.

Antibiotics can be a form of treatment, but the growing resistances of pathogens against antibiotics is a drawback. As a result, other forms of treating or preventing illness from food borne pathogens are being sought. Enhancement of human resistance to food-borne infections by functional food ingredients is therefore an attractive option.

An option to study the health benefits of functional food ingredients is to use a challenge study with a live, but attenuated, oral diarrhoeagenic E.coli strain, able to survive gastrointestinal transit and still able to induce mild (and short-lived) infection symptoms.
Although the existing diarrhoeagenic E. coli challenge model is already suitable for dietary interventions in its current form, further characterization of the working-mechanism of the attenuated strain and further optimization of the study design will enable us to better select those interventions that affect the key pathophysiological processes of infection.

Study objective

Primary Objective:
In the CORAL study we want to determine whether increasing the inoculation dose of diarrhoeagenic E. coli to 5*10^10 CFU and addition of a second challenge 1*10^10 CFU will result in an increased effect-size and duration of measurable outcomes and in an expansion of the relevant clinical and biomarker readouts of the challenge model.

Secondary Objective:
In addition, we want to determine whether adding extended fasting and addition of a standardized evening meal, prior to the inoculation day, will result in a decreased between-subject variation.

Study design

The CORAL study is a parallel 7-weeks intervention study. Subjects will be randomly assigned to one of two inoculation dosages of a live attenuated diarrhoeagenic E. coli (n=22 per group). Subjects will be instructed to maintain their usual pattern of physical activity and their habitual food intake, but to standardize their dietary calcium intake. After a standardized evening meal and an overnight fast, subjects will be orally infected with a

live, but attenuated, diarrhoeagenic E. coli (strain E1392-75-2A; collection NIZO food research; dose will be either 1*10^10 CFU (n=22) or 5*10^10 CFU (n=22). At a later stage in the study, all subjects will receive a second inoculation of 1*10^10 CFU of the ETEC vaccine (n=44).

Intervention

After a standardized evening meal and an overnight fast, subjects will receive a single oral dose of the attenuated diarrhoeagenic E. coli strain E1392-75-2A (dose will be either 1*10^10 CFU (n=22) or 5*10^10 CFU (n=22)).

At a later stage, all subjects will receive a second inoculation 1*10^10 CFU of the diarrhoeagenic E. coli.

Subjects will be instructed to maintain their habitual diet, except for their dairy intake. Dietary guidelines will limit calcium intake on average to 500 mg/day.

Study burden and risks

Over the past 40 years, the enterotoxigenic E. coli (ETEC) human challenge model has been used to elucidate the pathogenesis and immune responses associated with ETEC infection as well as to test the efficacy of investigational drugs and vaccines. A systematic review of the published and unpublished literature to evaluate specific outcomes in subjects participating in experimental ETEC infection studies using the accepted principles of good methodological design was published previously by Porter et al (2011). Unlike the strains used in this systematic review, the strain used at NIZO food research, is a spontaneous mutant unable to produce toxins. The basic concept of the diarrhoeagenic E.coli strain challenge study we have developed at NIZO food research is that we have selected a well-characterized, antibiotic susceptible organism that has been associated with very mild diarrhoea and gastrointestinal symptoms (severity and duration). All recorded disease episodes were self-limiting and did not require early antibiotic treatment.

Contacts

Public
NIZO food research

Kernhemseweg 2
Ede 6718ZB
NL
Scientific

NIZO food research

Kernhemseweg 2
Ede 6718ZB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Ability to follow verbal and written instructions;
2. Age between 18 and 55 years;
3. Availability of internet connection;
4. BMI >=20 and <=27 kg/m2;
5. Healthy as assessed by the NIZO food research medical questionnaire;
6. Male subjects;
7. Signed informed consent;
8. Voluntary participation;
9. Willing to accept disclosure of the financial benefit of participation in the study to the authorities concerned;
10. Willing to accept use of all encoded data, including publication, and the confidential use and storage of all data for at least 15 years;
11. Willing to comply with study procedures;
12. Willingness to abstain from high calcium containing products.
13. Willingness to abstain from medications that contain acetaminophen, aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs, (OTC) antacids and antimotility agents (eg, loperamide) on the three days before, during and 3 days after diarrhoeagenic E. coli challenge.
14. Willingness to abstain from alcoholic beverages three days before, during and three days after diarrhoeagenic E. coli challenge.
15. Willingness to give up blood donation starting 1 month prior to study start and during the entire study;

Exclusion criteria

1. Disease of the GI tract, liver, bile bladder, kidney, thyroid gland (self-reported);
2. Diarrhoeagenic E.coli strain (as used in the study) detected in fecal sample at screening;
3. Evidence of current excessive alcohol consumption or non-therapeutic drug (ab)use);
4. Evidence of IgA deficiency (serum IgA < 7 mg/dL or below the limit of detection of assay).
5. High titer serum antibodies against CFA-II diarrhoeagenic E.coli strain (as used in the study) at screening;
6. History of microbiologically confirmed ETEC or cholera infection in last 3 years.
7. Known allergy to the following antibiotics: ciprofloxacin, trimethoprim-sulfamethoxazole, and penicillins.
8. Mental status that is incompatible with the proper conduct of the study;
9. Not having a general practitioner, not allowing disclosure of participation to the general practitioner or not allow to inform the general practitioner about abnormal results.
10. Occupation involving handling of ETEC or Vibrio cholerae currently, or in the past 3 years.
11. Participation in any clinical trial including blood sampling and/or administration of substances starting 1 month prior to study start and during the entire study;
12. Personnel of NIZO food research, their partner and their first and second degree relatives;
13. Reported average stool frequency of <1 or >3 per day;
14. Symptoms consistent with Travelers' Diarrhoea concurrent with travel to countries where ETEC infection is endemic (most of the developing world) within 3 years prior to dosing, OR planned travel to endemic countries during the length of the study.
15. Use of antibiotics, norit, laxatives (up till 6 months prior to inclusion), cholestyramine, antacids, H2 receptor antagonists or proton pump inhibitors or immune suppressive agents (up till 3 months prior to inclusion);
16. Vaccination for or ingestion of ETEC, cholera, or E coli heat labile toxin within 3 years prior to inclusion;
17. Vegetarians and vegans

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-01-2016
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO

Date:	01-09-2015
Application type:	First submission
Review commission:	METC Wageningen Universiteit (Wageningen)

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	NL54064.081.15