Multicentre, Randomised, Placebo-Controlled Trial of Mebeverine in Children with Irritable Bowel Syndrome (IBS) or Functional Abdominal Pain- Not Otherwise Specified (FAP-NOS)

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The primary objective of this study is to determine the effect of mebeverine on abdominal pain intensity and frequency in children with irritable bowel syndrome or functional abdominal pain - not otherwise specified.

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

Summary

ID

NL-OMON55563

Source
ToetsingOnline

Brief title
Duski

Condition

- Gastrointestinal motility and defaecation conditions

Synonym
functional abdominal pain - not otherwise specified, irritable bowel syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Mylan. Bijdrage: ¤70.000,Stichting Kindermotiliteit;Emma Kinderziekenhuis;AMC

Intervention

Keyword: Children, Efficacy, Irritable Bowel Syndrome, Mebeverine

Outcome measures

Primary outcome

The primary outcome is the proportion of patients with at least 50% reduction of their abdominal pain intensity and frequency at the end of treatment (12 weeks). The main goal in the treatment of patients with IBS or FAP-NOS is reduction of abdominal pain and therefore pain is our primary outcome. Severity of abdominal pain will be assessed using a diary card, on which patients record daily intensity on a 6 point Likert scale and frequency of abdominal pain episodes during a period of 7 consecutive days. Recording of pain during 7 days is elaborate, but has the benefit that the problem of individual variability in symptoms over time will be reduced. This 7-day diary recording will be done (I) at the start of the baseline period, (II) in the fourth week of the study (start of treatment), (III) in the eight week, (IV) at the twelfth week (end of treatment) and (V) four weeks after the end of treatment.

Secondary outcome

Secondary outcomes of this study are to investigate the effect of mebeverine on other outcome parameters such as adequate relief, quality of life, depression and anxiety scores, and school absenteeism in children, to investigate the effect of reassurance, explanation and simple dietary and behavioural advice,

to study the influence of labelling on the effect of both mebeverine and placebo on pain scores, to study the effect of mebeverine on the faecal gut microbiota composition and to determine the safety of mebeverine in children with irritable bowel syndrome or functional abdominal pain - not otherwise specified. These secondary outcomes will be measured at the start of the baseline period and at the end of treatment.

Study description

Background summary

Chronic abdominal pain due to irritable bowel syndrome (IBS) or functional abdominal pain - not otherwise specified (FAP-NOS) is common in children, resulting in a reduced quality of life and associated with a higher risk of depression and anxiety. The first line of standard medical care for chronic abdominal pain consists of explanation, reassurance, dietary advice and painkillers if needed. The effect of this therapy has not been investigated thoroughly. Apart from the painkillers, mebeverine is also often prescribed by general practitioners and paediatric gastroenterologists for children with IBS or FAP-NOS. Mebeverine is a spasmolytic agent. In adults studies have been done to assess the efficacy of this agent, but in children these studies are lacking, even though mebeverine is already registered for the use in children above 10 years.
The setting of an RCT is not comparable to daily practice in which patients know that they are given an active drug. Information provided to patients is thought to influence placebo and drug effects. To date, the influence of labelling hasn*t been tested in children.

Study objective

The primary objective of this study is to determine the effect of mebeverine on abdominal pain intensity and frequency in children with irritable bowel syndrome or functional abdominal pain - not otherwise specified.

Study design

In this multicenter trial 284 children, aged between 12 and 18 years, with IBS or FAP-NOS according to the Rome IV criteria will be included.
This multicentre study starts with a baseline observation period of four weeks

in which patients are treated according to the first line of treatment for IBS or FAP-NOS. This standard medical therapy consists of reassurance, explanation and simple dietary and behavioural advice. During the baseline observation period no mebeverine or placebo and not any other drug influencing gut motility is given. After this 4-week period the patients who achieve adequate relief according to their parents with the standard medical treatment will be excluded. The remaining patients will start an 8-week randomised double-blind treatment period with either placebo or mebeverine. Half of the patients randomised to either placebo or mebeverine, will be told that they will receive the active drug. This results in a labelled drug. With this design of the study, the therapeutic effect of positive labelling on abdominal pain will be measured. The primary outcome is the proportion of patients with at least 50% reduction of their abdominal pain intensity and frequency at the end of treatment (12 weeks). The expected percentage of success after 8 weeks of medication therapy in the unlabelled mebeverine group is 65% and the expected percentage is 40% in the unlabelled placebo group. Equal group sizes of 62 achieve 80% power to detect a significant difference between groups using a two-sided Chi-square test without continuity correction and with a significance level of 0.05. Since we expect 10% to 15% dropout, a minimum of 71 per unlabelled treatment group will be included. To investigate the influence of labelling on outcome, we need two additional groups who will receive *open label* mebeverine or *open label* (labelled as mebeverine) placebo. As far as we know there is only one study assessing this two conditions, but this study has been conducted in adults. We believe we cannot use their results with respect to the difference in suggestibility between children and adults. Therefore we must make reasonable estimates, resulting in a difference of 25% on outcome between the unlabelled- and the labelled-group in both treatment arms which we consider as clinically relevant. Using the exact calculation as described above, we likewise have to include a minimum of 71 per labelled treatment group. Consequently we will need 284 patients for this trial. Secondary outcomes of this study are to investigate the effect of mebeverine on other outcome parameters such as adequate relief, quality of life, depression and anxiety scores, and school absenteeism in children, to investigate the effect of reassurance, explanation and simple dietary and behavioural advice, to study the influence of labelling on the effect of both mebeverine and placebo on pain scores, to study the effect of mebeverine on the faecal gut microbiota composition and to determine the safety of mebeverine in children with irritable bowel syndrome or functional abdominal pain - not otherwise specified.

Intervention

This multicentre study starts with a baseline observation period of four weeks in which patients are treated according to the first line of treatment for IBS or FAP-NOS. This standard medical therapy consists of reassurance, explanation and simple dietary and behavioural advice. During the baseline observation period no mebeverine or placebo and not any other drug influencing gut motility

is given. After this 4-week period the patients who achieve adequate relief according to their parents with the standard medical treatment will be excluded. The remaining patients will start an 8-week randomised double-blind treatment period with either twice a day a placebo or twice a day mebeverine. Half of the patients randomised to either placebo or mebeverine, will be told that they will receive the active drug. This results in 4 groups: the unlabelled mebeverine group, the labelled mebeverine group, the unlabelled placebo group and the labelled placebo group.

Study burden and risks

During the first consult a full patients history and a thorough physical examination will be done. Blood and feces tests will be performed to exclude organic causes for the abdominal pain, if this hasn*t been done recently by the general practitioner. When patients fulfill the Rome IV criteria for either functional abdominal pain - not otherwise specified or irritable bowel syndrome they will be invited to participate in the study. At the start of the baseline period, the children and parents will complete three questionnaires. In addition, they will record the severity of their abdominal pain concerning the preceding week on a pain diary card. All the participants will receive the first part of standard medical care for IBS or FAP-NOS during the first four weeks. After this 4-week period the patients who achieve adequate relief according to their parents with the standard medical treatment will be excluded. The remaining patients will start an 8-week randomised double-blind treatment period with either a placebo or mebeverine. We will ask all the randomised participants to record the severity of their abdominal pain on a pain diary card again on week 8 (seen from baseline), week 12, week 16 and week 36. Furthermore we will ask the children and the parents to fulfill three questionnaires at week 12 and week 36 and one last questionnaire at week 16. Eventually, we will ask the children to bring some morning stool samples at baseline (week 0), 4 weeks and 12 weeks.
There are hardly any risks for the participating children in this study. Studies in adults assessing the efficacy and safety of mebeverine show it is safe to use. Apart from that, the experience of prescribing mebeverine for children for several years has learned us that there is a very small risk of side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

All children aged between 12 and 18 years diagnosed with irritable bowel syndrome or functional abdominal pain - not otherwise specified according to the Rome lV criteria and where informed consent, given by both parents and by children aged 12 years and older, is available, will be invited to participate.
The Rome lV criteria form the internationally accepted standard for defining functional gastrointestinal disorders like irritable bowel syndrome and functional abdominal pain-not otherwise specified. Before inclusion, all patients undergo routine laboratory testing to exclude underlying organic disorders: complete blood cell count, C-reactive protein, celiac screening (anti-transglutaminase antibodies and IgA), and fecal calprotectin.
Finally, according to a recently published guideline by the Rome Foundation for the design of pharmacological clinical trials in children, patients are required to have an average daily pain rate of >=2 on the Wong Baker Faces Pain Scale

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

• Current treatment by another health care professional for abdominal symptoms
• Previous use of mebeverine
• Known hypersensitivity to the active substance or to any of the excipients (magnesium stearate, polyacrylate dispersion, talc, hypromellose, methacrylic acid - ethyl acrylate copolymer (1:1) dispersion, glycerol triacetate, gelatine, titanium dioxide (E171), shellac (E904), propylene glycol, ammonia solution (concentrated), potassium hydroxide, iron oxide black (E172)).
• Known diagnosis of cystic fibrosis
• Known diagnosis of porphyria
• Known concomitant organic gastrointestinal disease
• Current use of drugs which influence gastrointestinal motility, such as erythromycin, azithromycin, domperidone, and Iberogast (current use of drugs which influence gastrointestinal motility may be met as long as the subject is on a stable dose and the dose will not be adjusted during the study.
• Insufficient knowledge of the Dutch language
• Known pregnancy or current lactation

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-11-2018
Enrollment:	284
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Duspatal
Generic name:	Mebeverine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-12-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2020
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

ID: 23931
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2015-003293-32-NL
CCMO	NL55301.018.15
Other	Trial NL7508
OMON	NL-OMON23931