Prevention of opioid-induced constipation in patients with advanced cancer

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This study has been transitioned to CTIS with ID 2023-509462-38-00 check the CTIS register for the current data. Primary Objective: In patients with advanced cancer, starting with opioids for pain: • To prove non-inferiority of magnesium hydroxide...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal signs and symptoms
Study type	Interventional

Summary

ID

NL-OMON53756

Source
ToetsingOnline

Brief title
OMAMA-study

Condition

- Gastrointestinal signs and symptoms

Synonym
constipation

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: advanced cancer, constipation, opioids, pain

Outcome measures

Primary outcome

The primary endpoint is constipation, defined as the percentage of patients

with a score of <30 of the Bowel Function Index, measured on day 14.

Secondary outcome

• Change of the Bowel Function Index Score between day 0 and day 14;

• Quality of life;

• Rome IV criteria for opioid-induced constipation as judged by professional

care givers

• Cancer pain score

• Patient satisfaction with laxative;

• Side effects of laxatives;

• Cost-effectiveness of macrogol/electrolytes compared to magnesium hydroxide

Study description

Background summary

More than 70% of patients with metastatic cancer have pain that often requires treatment with opioids (morphine-like agents) (Teunissen 2007). Constipation occurs in 59% of patients treated with opioids (Davies 2021). Opioid-induced constipation (OIC) has a significant negative effect on the quality of life of patients, due to physical problems, psychological problems and social consequences (Bell 2009, Christensen 2017, Davies 2021, Dhingra 2013, Penning-van Beest 2010). It has consequences that range from daily discomfort with social insecurity and disability to intestinal obstruction. It leads to limitations in self-management, a reduced quality of life and a risk of need for more care, including hospital admission. Standard laxatives are recommended

to prevent OIC, although there is little evidence to support this (Farmer 2019). There have been only two randomised studies with laxatives in symptomatic OIC (Freedman 1999, Hawley 2020). Freedman (1999) performed a double-blinded randomised study in 57 drug-dependent men and women with OIC receiving methadone, comparing macrogol/electrolytes with lactulose and placebo. Macrogol/electrolytes and lactulose produced more *nonhard* stools than the placebo (P<0.01) and baseline(P <0.003). There was no statistically significant difference between macrogol/elektrolytes and lactulose. Macrogol/electrolytes produced the loosest stool (P<0.0001) compared with baseline, whereas lactulose had the most adverse effects. Hawley (2020) compared macrogol/electrolytes with sennosides in a randomised, double-blind, double-dummy cross-over study in 70 cancer patients (of whom 42 completed the first treatment) at risk or already experiencing OIC. She found weak evidence that macrogol/electrolytes was superior to sennosides in terms of more days with a satisfactory bowel movement during three weeks of treatment. A recent review found moderate benefit for osmotic or stimulant laxatives for patients with cancer and symptomatic OIC (Ginex 2020). Magnesium hydroxide is registered as an antipeptic drug, but also used as a laxative (but not registered for this indication). In the past and in previous studies magnesium oxide was used. As magnesium oxide is transformed in the stomach tot magnesium hydroxide, these drugs are considered to be the same. Presently, only magnesium hydroxide is prescribed in The Netherlands. There have been no studies on magnesium (hydr)oxide in symptomatic OIC. There have been no randomised studies about prevention of OIC by magnesium (hydr)oxide. Two prospective non-randomised studies compared the prevalence of OIC after 14 days with or without prophylactic laxatives (mostly magnesium oxide): 48% versus 65% (Tokoro 2019, prospective study) and 34% versus 55% (Ishihara 2012). Thus, approximately 60% of patients starting with opioids and not using laxatives will develop constipation and 40% will not. Dutch guidelines on pain in cancer patients (2019, www.pallialine.nl) and constipation in palliative care patients (2010, www.pallialine.nl) recommend either macrogol/electrolytes or magnesium hydroxide as first-line laxative treatment to prevent OIC. The guideline on constipation in palliative care patients is currently being revised. The preliminary advice of the concept guideline is unchanged. Thus, macrogol/electrolytes has been proven to be effective for symptomatic OIC based on two randomised studies (Freeman 1999, Hawley 2020) and is registered for this indication. However, it has not been proven to be effective for prevention of OIC and is not explicitly registered for this indication. It is sometimes perceived by patients as unpleasant due to its taste. For magnesium oxide retrospective data are available (Ishihara 2012, Tokoro 2019), suggesting that it may prevent OIC and it has a neutral taste. Although it is also recommended by the guideline, it has not been registered for the treatment or prevention of constipation. To support the advice of the guideline and to prove that a choice is possible, it is important to demonstrate that magnesium hydroxide is not inferior to macrogol / electrolytes and to compare side-effects and tolerability.

Study objective

This study has been transitioned to CTIS with ID 2023-509462-38-00 check the CTIS register for the current data.

Primary Objective: In patients with advanced cancer, starting with opioids for pain: • To prove non-inferiority of magnesium hydroxide to macrogol/electrolytes in the prevention of OIC, based on the percentage of patients without obstipation (BFI-score <30) after 14 days of treatment. Secondary Objectives: In patients with advanced cancer, starting with opioids for pain: • To compare magnesium hydroxide with macrogol/electrolytes with regard to the Rome IV criteria after 14 days of treatment; • To compare magnesium hydroxide with macrogol/electrolytes with regard to quality of life (as measured with the EQ5D) after 14 days of treatment; • To compare magnesium hydroxide with macrogol/electrolytes with regard to side effects and patient satisfaction with laxative after 14 days of treatment; • To compare magnesium hydroxide with macrogol/electrolytes with regard to difference in pain score between laxative treatment after 14 days of treatment; • To compare magnesium hydroxide with macrogol/electrolytes with regard to comparative cost-effectiveness; • To predict non-resp[onders by gender, age, BMI, site of cancer, site of metastases and use of medication.

Study design

A randomized, open-label study during 14 days (days 1-14). After informed consent (maximally a day after the start of the opioid), randomization (locally), stratified per centre, will be performed between macrogol/electrolytes and magnesium hydroxide.
Patients with advanced cancer starting with opioids for pain will be included from the departments of medical oncology, pulmonology and radiotherapy of both academic and non-academic hospitals in The Netherlands.
This study is considered to be a low-intervention trial according to European Union regulation no. 536/2014 of the European parliament and of the Council of the European Union (https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf). .

Intervention

Randomization between macrogol/electrolytes or magnesium hydroxide to prevent OIC at the start of treatment with opioids for a treatment period of 14 days. Macrogol/electrolytes is started at a dose of 1 sachet once daily and magnesium hydroxide at a dose of 724 mg t.i.d., both orally. Macrogol/electrolytes is regarded as the standard treatment (usual care) to which magnesium hydroxide will be compared. The dose of macrogol/electrolytes and magnesium hydroxide may be increased to 2 sachets daily and 1448 mg t.i.d., respectively, or may be

decreased during the study period. Macrogol/elektrolytes and magnesium hydroxide may also be discontinued during the study period.

Study burden and risks

The burden and risks of the study are expected to be minimal. The patients receive the same treatment as in regular practice. They have to complete two questionnaires, taking about 15 minutes per questionnaire.
OIC has a significant negative effect on the quality of life of patients, due to physical problems, psychological problems and social consequences. The results of this study will lead to better prevention of OIC in patients with advanced cancer using opioids for pain, leading to better quality of life. Possibly, it may also lead to better pain control, as opioid treatment will be less hampered by dose reductions or changes of pain treatment due to constipation. Finally, it may lead to registration of magnesium hydroxide for this indication.
The study can only be performed using these patient groups.

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 advanced cancer (>=18 years);
• Starting with slow release or transdermal opioids for pain;
• Able to complete a Dutch questionnaire.
Previous treatment with opioids is allowed, if discontinued more than 4 weeks ago.

Exclusion criteria

• Patients with contra-indications for laxatives • Maintenance treatment with laxatives during the last two weeks • Severely impaired renal function (serum creatinine >180 umol/l) • Estimated life expectancy <1 month

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-12-2022
Enrollment:	330
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	?
Generic name:	macrogol/electrolytes
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	?
Generic name:	magnesium hydroxide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-09-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2023

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2024
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
EU-CTR	CTIS2023-509462-38-00
EudraCT	EUCTR2022-000408-36-NL
ClinicalTrials.gov	NCT05216328
CCMO	NL80508.029.22