Neurotoxic adverse effects of morphine and oxycodone in continuous subcutaneous infusion for treatment of pain in terminal patients with diminished renal function: a Randomized Controlled Trial.

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The primary objective of this study is to compare the prevalence of delirium between oxycodone and morphine, administered by CSCI, for the treatment of pain in dying patients with a diminished renal function.The secondary objective is to compare the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Therapeutic and nontherapeutic effects (excl toxicity)
Study type	Interventional

Summary

ID

NL-OMON44278

Source
ToetsingOnline

Brief title
MOSART-study

Condition

- Therapeutic and nontherapeutic effects (excl toxicity)
- Deliria (incl confusion)
- Renal disorders (excl nephropathies)

Synonym
neurotoxic adverse effects, unwanted effects on the nervous system

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: ZonMW,Envida

Intervention

Keyword: Adverse effects, Morphine, Oxycodone, Renal Insufficiency

Outcome measures

Primary outcome

The main study parameter is the difference in occurrence of delirium at any time between start of CSCI of morphine or oxycodone and death.

The Delirium Observation Screening (DOS)-scale is used for screening for presence for delirium. The clinical diagnosis of delirium is confirmed or rejected in accordance with the DSM-IV-TR criteria.

Secondary outcome

The secondary parameter is the difference in occurrence of allodynia/hyperalgesia at any time between start of CSCI of morphine or oxycodone and death.

Brushing with a piece of cotton wool on the skin and pin-prick testing is performed to assess for presence of allodynia/hyperalgesia. Items of the Rotterdam Elderly Pain Observation Scale (REPOS) are used to determine presence of pain in subjects who are verbally inadequate responsive.

Study description

Background summary

The prevalence of significant pain at the end of life is high. Continuous subcutaneous infusion (CSCI) of opioids is the cornerstone in treatment of pain in this last phase of life. Although morphine is the most frequent used opioid in this respect, its main metabolites * morphine-3-glucuronide (M3G) and morphine-6-glucuranide (M6G) * start to accumulate when renal function decreases. The accumulation of M3G is associated with neurotoxic adverse effects like delirium, allodynia and hyperalgesia. The central effects of circulating metabolites of oxycodone, on the other hand, are negligible. On theoretical considerations CSCI of oxycodone for the treatment of pain in dying patients with a diminished renal function should therefore result in a reduced occurrence of the neurotoxic adverse effects delirium and allodynia/hyperalgesia in comparison to morphine. However, studies of sufficient quality investigating the clinical effect of this hypothesis are lacking at the moment.

Study objective

The primary objective of this study is to compare the prevalence of delirium between oxycodone and morphine, administered by CSCI, for the treatment of pain in dying patients with a diminished renal function.

The secondary objective is to compare the prevalence of allodynia/hyperalgesia between these two opioids.

Study design

A randomized, controlled, observer blinded, multicentre, superiority trial with to parallel groups with an 1:1-allocation-ratio.

Intervention

One group receives CSCI of oxycodone and the other group CSCI of morphine.

Study burden and risks

Since the investigated products are registered products to be used in regular care for the registered indication and route of administration, and not in combination with other products, participants are not exposed to any additional medication-related risks. A one-time blood collection by venipuncture at the first visit is performed to assess renal function. The risk of venepuncture-related complications is considered low. The burden associated

with assessment for delirium and allodynia/hyperalgesia three times a week is considered low. It is essential to not exclude an incapacitated (psychogeriatric) population in this study to best represent usual care, since the major part of dying patients experiences a decline in cognitive functions and are not able to respond adequately anymore. Special attention will be paid to signs of objection or resistance to any of the study procedures by incapacitated subjects.

Contacts

Public
Medisch Universitair Ziekenhuis Maastricht

P. Debyelaan 25
Maastricht 6229 HX
NL
Scientific
Medisch Universitair Ziekenhuis Maastricht

P. Debyelaan 25
Maastricht 6229 HX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- minimal age of 18 years at the time of inclusion;
- the subject is in the terminal phase, i.e. death in the near future is expected by the treating physician;

- start of CSCI with an opioid for treatment of pain is indicated by the treating physician;
- willingness to allow one-time blood collection for assessment of renal function (eGFR);
- a signed informed consent is given by the participant or his/her legal representative.

Exclusion criteria

- delirium at the time of inclusion;
- opioid induced hyperalgesia (OIH) at the time of inclusion;
- a medical necessity to apply a different opioid than morphine or oxycodone, such as previously demonstrated non-response to morphine or oxycodone (defined as a complete absence of any pain reduction after appropriate dosage), previously demonstrated unacceptable side effects of morphine or oxycodone, or a medical indication for an opioid with NMDA-receptor-antagonistic properties (currently only known for methadone);
- a documented allergy for morphine or oxycodone.;Subjects with an eGFR >50 ml/min/1.73m2 should not be included in the study, because accumulation of metabolites is considered to be irrelevant in this range of renal functions. Despite this fact, we cannot formulate an unaffected renal function as an exclusion criterion prior to allocation, because the time needed for assessment of the renal function could lead to either an unethical delay in treatment of pain or occurrence of death even before the lab results are known. Therefore renal function is assessed after inclusion. In case a subject turns out to exceed the threshold of 50 ml/min/1.73m2, this will be considered as meeting an extended exclusion criterion and the subject concerned will be replaced by a new subject.

Study design

Design

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

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	04-06-2018
Enrollment:	351
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	only generic products
Generic name:	morphine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	only generic products
Generic name:	oxycodone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-07-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-12-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
EudraCT	EUCTR2017-002192-25-NL
CCMO	NL62110.068.17

Study results

Date completed: 01-02-2019

Actual enrolment: 3

Summary results
Trial ended prematurely