A MR30365/07 dose-ascending, cohort group, single-blind pilot phase followed by a randomised, double-blind, placebo controlled parallel group study to compare the effect of intravenous MR30365/07 and intravenous fentanyl on respiration and analgesic responses, in healthy volunteers.

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

Summary

ID

NL-OMON39453

Source
ToetsingOnline

Brief title
MR30365/07 respiration and analgesic response study

Condition

- Other condition

Synonym
respiration; analgesic response

Health condition

ademhaling en pijnstilling

Research involving
Human

Sponsors and support

Primary sponsor: Mundipharma Research Limited
Source(s) of monetary or material Support: Mundipharma Research Limited;UK

Intervention

Keyword: Analgesic response, MR30365/07, Respiration

Outcome measures

Primary outcome

Pilot phase:

To determine the MR30365/07 doses to be used in the main study based on

respiratory responses and safety data

Main phase:

To obtain a dose-response relationship for MR30365/07*s analgesic and

respiratory effects and compare these relationships with those of fentanyl and

placebo.

Secondary outcome

Pilot phase:

To assess safety and tolerability of MR30365/07

Main phase:

To assess safety and tolerability of MR30365/07 compared to fentanyl and

placebo. To assess the PK of MR30365/07 and fentanyl

Study description

Background summary

MR30365/07 and fentanyl are opioid analgesics.
Respiratory depression is a common side effect with opioids. This study is to assess the effect of MR30365/07 on ventilation and antinociception compared to fentanyl and placebo.

Study objective

The aim of the main study is to compare the effects of MR30365/07 and fentanyl on ventilation and analgesic responses to noxious electrical and heat stimulation in healthy volunteers, by performing pharmacokinetic / pharmacodynamics (PK/PD) modeling.

Study design

A pilot phase will be performed prior to the main study In order to determine the MR30365/07 doses, based on respiratory responses and safety data, to be used In the main study. In the main the subjects were randomised into 2 groups, the respiratory group to assess the effects on ventilation and the analgesia group to assess the effects on anti-nociception. A single 10 minute infusion of study medication was administered to each subject in a semi-supine position. Safety assessments and respiratory measurements were recorded following each study medication administration.

Intervention

Pilot Phase (9 subjects - respiratory measurements and safety assessments):
After screening the subjects were allocated into 3 cohort groups. Each subject received a single infusion of MR30365/07 on 3 occasions in dose-ascending order, and a single infusion of placebo. Therefore, subjects received 4 doses of study medication in total. Respiratory and safety assessments were performed. The MR30365/07 doses tested in the pilot phase were 0.0125 µg/kg, 0.025 µg/kg, 0.05 µg/kg, 0.075 µg/kg, 0.1 µg/kg, 0.125 µg/kg and 0.15 µg/kg. There was a minimum of 7 day wash out period between the study drug dosing. Safety measurements were performed up to 24 hours post-dose and the subjects

returned for a post-medical visit 4-7 days after the last dose of the study drug in case of completion/discontinuation from the study.

Main Phase (Respiratory and Analgesia Groups - 46 subjects per group):
Based on the data from the pilot phase the optimal concentrations of MR30365/07 to administer in the main phase were 0.0125, 0.075, 0.125 and 0.15 µg/kg MR30365/07. After screening the subjects were allocated to a respiratory (n=46 subjects) or analgesia group (n=46 subjects) to receive a single 10 minute infusion of MR30365/07, fentanyl or placebo on one occasion according to a RAS. The appropriate PK, PD and safety assessments were performed for each subject.

Concentration (ug/kg) Number of
Subjects (Respiratory) Number of Subjects (Analgesia)
Fentanyl 0.5 4 4

1
6
6

2 6
6 3 4 4
MR30365/07 0.0125
4 4
0.075
6
6
0.125
6 6
0.15
4 4

Placebo

0 6 6

Predefined stopping rules were applied in the pilot and the main phase:
• Apnoea, defined as discontinuation of rhythmic breathing for 1 minute
• pCO2 > 9 KPa
• O2 saturation 85% or less
• Increase in QTc of more than 60 msec above pre-dose values of each study period or
QTc greater than 500 msec
• Serious adverse drug reaction.
If a subject experienced any of the above they were discontinued from the

study. If 2 subjects experienced any of the above the cohort was not further dosed and the next cohort was not proceeded.

Study burden and risks

All subjects will have a screening visit and a post-study medical visit to confirm healthy status before entering the study and after receiving study treatment. Subjects in the pilot phase will have 4 treatment visits (placebo on one occasion and MR30365/07 on 3 occasions). Subjects in the main study will have one treatment visit (MR30365/07, fentanyl, or placebo). Subjects will remain in the clinic for 24 hours after receiving a 10 minute infusion. In the pilot phase there will be a 7-day washout before receiving their next dose. While in the clinic subjects will have regular measurements of vital signs, ECG, pulse oximetry and complete questionnaires. Respiratory tests involving wearing breathing apparatus or analgesic tests (heat or electrical pain) will be performed up to 8 hours post-dose. Headache may be experienced during or after the respiratory test. In the main study, an arterial line will be used to collect blood samples over 24 hours for pharmacokinetic analysis.
Typical opioid side effects would be expected such as nausea, feeling of heaviness, itching/skin rush at infusion site. One of the side effects that may occur is respiratory depression. If unexpected severe respiratory depression occurs, the experiment will be stopped. Naloxone may be administered, which reverses the effect of MR30365/07. Extra oxygen may also then be administered to help breathing.
After the infusion into the vein has been removed a bruise may appear, which usually disappears by itself after a few days. This may also occur after blood sampling via the arterial line. There is no intended clinical benefit to the subject from taking part in the study.

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

Healthy male subjects aged 18 to 45 inclusive.
Healthy and free of significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG. Normal lung function test (FEV1>85% of predicted normal value).

Exclusion criteria

In the Investigator*s opinion a clinically significant upper or lower respiratory infection within 4 weeks prior to the screening visit. History of asthma, COPD, or other bronchial or lung diseases. History of regurgitation or difficulty of intubation. History of additional risk factors or Torsades de Pointes. Abnormal cardiac conditions (QTc Interval greater than 450msec at screening or pre-dose). Known sensitivity to fentanyl, opioids, ondansetron, naloxone, or related compounds.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-07-2010
Enrollment:	111
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fentanyl Bipharma
Generic name:	fentanyl solution
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MR30365/07
Generic name:	MR30365/07

Ethics review

Approved WMO Date:	04-02-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-04-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-02-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-02-2012

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-010880-17-NL
CCMO	NL30986.058.10