RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE ESCALATION STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF SINGLE AND MULTIPLE DOSES OF 2-IMINOBIOTINE (2-IB) IN HEALTHY MALE SUBJECTS

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Primary objectives- to investigate the safety and tolerability of single and multiple doses of 2-IB pulse iv infusion in healthy male subjects - to determine the pharmacokinetics after single and multiple doses of 2-IB pulse iv infusion in healthy...

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

Summary

ID

NL-OMON35086

Source
ToetsingOnline

Brief title
First-in-human 2-IB dose escalation study

Condition

- Foetal complications

Synonym
Oxygen deprivation

Research involving

Human

Sponsors and support

Primary sponsor: Neurophyxia B.V.
Source(s) of monetary or material Support: Farmaceutische Industrie.

Intervention

Keyword: 2-IB, 2-Iminobiotin, perinatal asphyxia

Outcome measures

Primary outcome

Pharmacokinetics:

plasma concentrations of 2-IB; PK parameters in plasma and urine: Cmax, tmax,

kel, t1/2, AUC0-t, AUC0 inf, %AUC, AUC0-4, CL, Vz, MRT, Ae0-t

Safety:

AEs, vital signs, 12-lead ECG, clinical laboratory, infusion site inspection

and physical examination

Secondary outcome

na

Study description

Background summary

The drug to be given 2-iminobiotin (2-IB), is a new, investigational compound that may eventually be used for the treatment of perinatal asphyxia (serious oxygen deprivation in a baby around the birth). The new drug is still under development.
Perinatal asphyxia is the medical condition resulting from deprivation of oxygen to a newborn infant long enough to cause apparent permanent harm. It results most commonly from a interference of the blood flow (ie. When the

umbilical cord is wrapped around the babies neck)..
2-iminobiotin (2-IB) is a selective nitric oxide synthase inhibitor which inhibits the chemical processes which are triggered after oxygen deprivation. It is expected that it may contribute to the treatment and prevention of the devastating effects of perinatal asphyxia.

Study objective

Primary objectives
- to investigate the safety and tolerability of single and multiple doses of 2-IB pulse iv infusion in healthy male subjects
- to determine the pharmacokinetics after single and multiple doses of 2-IB pulse iv infusion in healthy male subjects

Secondary objectives
-To investigate the safety and tolerability of multiple doses of a 5% Captisol® infusion
formulation in healthy male subjects
-To determine the effect of a 5% Captisol® infusion formulation on the safety and
pharmacokinetics of 2-IB
-To determine the pharmacokinetics after multiple doses of a 5% Captisol® infusion formulation in healthy male subjects*

Study design

Design:
A randomized, double-blind, placebo-controlled, dose escalation study with 2 groups of 9 healthy male subjects each receiving a pulsed intravenous (iv) infusion of 2-IB or placebo in 3 periods. Treatments will be randomized such that each subject receives 2 out of 3 foreseen dose levels of 2 IB and once placebo. There will be a washout period of at least 7 days between each dosing period. During Period 1 of Group 1, 3 subgroups (Groups 1a, 1b and 1c) of 3 subjects (2 on active and 1 on placebo) will be dosed. after the dosing of Cohort 1, there will be an interim PK evaluation to reconsider the dose-escalation and PK sampling for Cohort 2. In Cohort 2 a new formulation of the compound will be used in order to limit the IV volume as much as possible.

Procedures and assessments
Screening and follow-up:
Clinical laboratory, vital signs, physical examination, ECG; at eligibility screening: medical history, drug screen, HBsAg, anti HCV, anti-HIV 1/2; drug screen to be repeated upon each admission.

Observation period:
Group 1: 3 periods in the clinic; first period in clinic from -17 h up to 24 h

after start of first drug administration, second and third period in clinic from -17 h up to 48 h after start of the first drug administration
Group 2: 3 periods in the clinic; each period in clinic from -17 h up to 48 h after start of the first drug administration

Blood sampling:
for pharmacokinetics of 2-IB (Groups 1a, 1b, 1c and 2) and Captisol® (Group 2 only)in plasma: 11 time points after the start of the infusion (Cohorts 1a, b, c * Period 1), 9 time points after the start of the 1st and 3rd infusion (Cohort 1a, b, c * Periods 2 and 3), 9 time points after the start of the 1st and 3rd infusion (Cohort 2 * Period 1), 8 time points after the start of the 1stand 3rd infusion (Cohort 2 * Periods 2 and 3) and 11 time points after the last infusion (Cohort 1a, b, c * Periods 2 and 3 and Cohort 2 * Periods 1, 2 and 3)

Urine sampling:
For pharmacokinetics of 2-IB: Groups 1a, 1b and 1c, Period 1: in intervals of 0-4 h and 4 12 h after the start of the infusion, Groups 1a, 1b and 1c, Periods 2 and 3: in intervals of 20-24 h and 24-32 h after the start of the first infusion, Group 2: each period in intervals of
20-24 h and 24-32 h after the start of the first infusion.

Pharmacodynamic assessment:
Near infrared spectroscopy (NIRS): at pre-dose of the first infusion and at 15 min and 2.5 h after the start of the third infusion in Period 3 of Group 1 and in all periods of Group 2 (the timing of the NIRS assessments may be adjusted for subsequent groups based on the results).

Safety assessments:
Adverse events: throughout the study; vital signs: each period pre-first dose and at approximately 30 min after each infusion; ECG: each period pre-first dose and 6, 10, 24 (Cohorts 1 and 2), 30, 34 and 48 h (Cohort 2 only) after the start of the first infusion; clinical laboratory: 24 (Cohorts 1 and 2) and 48 h (Cohort 2 only) after the start of the first infusion; NIRS: training session on Day -1 (first period only) and pre-dose and 30 min and 4 h after start of first and last infusion, infusion site inspection at least twice after eacht infusion.

Bioanalysis:
analysis of plasma and urine samples for 2-IB (Groups 1a, 1b, 1c and 2) and Captisol® (Group 2 only) by the Sponsor using a validated liquid chromatography-mass spectrometry/mass spectrometry method*

Intervention

Study Medication
Active substance : 2-IB

Activity : unknown
Indication : unknown
Strength : for Groups 1a, 1b and 1c: 1.0 mg/mL in pH 4
citrate buffer
for Group 2:
4.0 mg/mL in pH 4 citrate buffer and 5% Captisol® *
Dosage form : i.v. infusion

Treatments
Group 1a
Period 1: a single iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) over 4 h on Day 1
Period 2: a 15-min iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) every 4 h on Day 1 (6 infusions in total)
Period 3: a 15-min iv infusion of 2 mg/kg 2-IB (n=2) or placebo (n=1) every 4 h on Day 1 (6 infusions in total)

Group 1b
Period 1: a single iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) over 1 h on Day 1
Period 2: a 15-min iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) every 4 h on Day 1 (6 infusions in total)
Period 3: a 15-min iv infusion of 2 mg/kg 2-IB (n=2) or placebo (n=1) every 4 h on Day 1 (6 infusions in total)

Group 1c
Period 1: a single iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) over 15 min on Day 1
Period 2: a 15-min iv infusion of 0.6 mg/kg 2-IB (n=2) or placebo (n=1) every 4 h on Day 1 (6 infusions in total)
Period 3: a 15-min iv infusion of 2 mg/kg 2-IB (n=2) or placebo (n=1) every 4 h on Day 1 (6 infusions in total)

Dosing starting at t = 0 h, t = 4 h, t = 8 h, t = 12 h, t = 16 h and t = 20 h in Periods 2 and 3.

Group 2
Period 1 : a 15-min iv infusion of 2 mg/kg 2-IB (n=6) or placebo (n=3) every 4 h on Day 1 (6 infusions in total)
Period 2 : a 15-min iv infusion of 6 mg/kg 2-IB (n=6) or placebo (n=3) every 4 h on Day 1 (6 infusions in total)
Period 3: a 30-min iv infusion of 12 mg/kg 2-IB (n=6) or placebo (n=3) every 4 h on Day 1 (6 infusions in total)*

Dosing starting at t = 0 h, t = 4 h, t = 8 h, t = 12 h, t = 16 h and t = 20 h in Periods 1, 2 and 3.

Study burden and risks

Procedures:
Pain, light bleeding, heamatoma, possibly an infection.

Medication:
As 2-iminobiotin (2-IB), will be administered to man for the first time in this study, to date adverse effects in man have not been reported. However, there have been extensive studies on the safety of 2-IB in rats, dogs and mini pigs. In these studies (very) high doses of 2-IB have been administered, following a similar scheme as in the present study, over 24 to 96 hour periods. These studies have shown that 2-IB was well tolerated up to the highest dose levels. Only mild adverse effect have been observed in the test animals that were most likely not related to 2-IB, and the results justify the administration of 2-IB in humans. Captisol is an adjuvant that has been administered in preclinical and clinical studies before and is also used in a number of already available drugs. From these studies it was concluded that Captisol is safe and has no significant biological effects.. The highest daily doses of Captisol administered in humans thus far was 35 gram (4 administrations of 5 minutes within 24 hours). Although the highest dose of Captisol used in this study will exceed the highest daily dose administered in humans thus far, no safety issues are expected of the new formulation since Captisol leaves the body quickly.

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, 18-55 years of age, BMI 18 and 28 kg/m2, total body weight does not exceed 90 kg, a good venous accessibility for both arms, non or moderate smoker

Exclusion criteria

Suffering from: hepatitis B, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study.

Study design

Design

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):	15-12-2009
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO Date:	18-11-2009
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2009
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-02-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2009-016799-60-NL
CCMO	NL30430.056.09