TIBOHCA: A phase II study to evaluate the safety, tolerability and pharmacokinetics of 2-Iminobiotin (2-IB) after out of hospital cardiac arrest

Published: 15-03-2016
Last updated: 19-04-2024

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

Summary

ID

NL-OMON47307

Source
ToetsingOnline

Brief title
TIBOHCA

Condition

- Cardiac arrhythmias
- Encephalopathies

Synonym
postanoxic encephalopathy; brain injury after cardiac arrest

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Neurophyxia

Intervention

Keyword: Out-of-hospital cardiac arrest, Pharmacokinetics

Outcome measures

Primary outcome

The main study parameters used for evaluating the short term safety and tolerability will be vital signs ((heart frequency and blood pressure) before and until 15 minutes after administration of the study drug and the need for intervention), biochemistry and haematology taken as part of the clinical protocol, and the occurrence of (Serious) Adverse Events ((S)AEs) until a maximum of 7 days on the ICU or until discharge from the ICU, whichever occurs earlier.

For evaluation of the pharmacokinetics profile of 2-IB six plasma samples will be taken and analysed. Pharmacokinetic parameters to be determined will include Cmax, AUC, Tmax, t1/2, clearance (Cl), and volume of distribution (Vd).

Secondary outcome

Secondary parameters that will be evaluated:

1. Short term efficacy as determined by biochemical markers NSE and s100b at 24h and 48h after OHCA.

2. Longer term safety as determined by the occurrence of SAEs until 30 days after OHCA including death.

3. Longer term efficacy as determined by the Cerebral Performance Category

(CPC) and IQCODE at 30 days after OHCA or alternatively the Adult Lifestyles

and Function Interview (ALFI) scale (by telephone).

Study description

Background summary

Following successful cardiopulmonary resuscitation (CPR) after out of hospital cardiac arrest (OHCA), 50% of the patients admitted to the Intensive Care Unit (ICU) die. Since most patients die due to brain damage sustained during cardiac arrest and the subsequent reperfusion phase, effective neuroprotective strategies could potentially improve neurological outcome. In animal experiments, 2-iminobiotin (2-IB), a selective neuronal and inducible nitric oxide synthase (NOS) inhibitor, given upon reperfusion has been shown to improve memory function in a four vessel occlusion model in rats. Since 2-IB has not shown any safety issues in preclinical and clinical studies, this drug may be an effective strategy for reducing neurological damage after cardiac arrest. Before embarking on large studies with efficacy as a primary endpoint in this population, safety, tolerability and pharmacokinetics of this treatment need to be established in an exploratory Phase II study.

Study objective

The primary objective of this study is to evaluate the short term safety and tolerability, and pharmacokinetic properties of 2-IB when administered to adult patients after OHCA.
Secondary objectives include safety and efficacy parameters at 30 days after OHCA.

Study design

A Phase 2 open-label, dose-escalation intervention study.

Intervention

The first cohort of eight patients will receive 2-IB in a dose of 0,055 mg/kg/dose every 4 h iv, 6 times (part A). In part B the second cohort of eight patients will receive a dose based on the kidney function assessed with the estimated glomerular filtration rate (eGFR). In both treatment groups no safety issues occured. In part C of the study the third group of eight patients will be treated with a three times increased dosage (compared to group B) based on the kidney function. With this step the safety and pharmacokinetics can be investigate optimally.

The DSMB has approved to move to the next dose level.

Study burden and risks

We consider the risk for the patients in this study as moderate (matig risico). No toxicity has been demonstrated in preclinical studies and no adverse reactions that could be attributed to 2-IB have been shown in a Phase I study in adult humans and a Phase II pilot safety study in newborns with perinatal asphyxia.
Based on this, using the NFU classification, the risk could be classified as negligible. Since the patient population is very vulnerable, however, we increased the risk classification to "moderate" (matig risico).
The extra burden of participation is limited, since most assessments done are part of standard clinical care. All patients will receive 2-IB using an existing intravenous catheter (central of peripheral) and will receive 6 doses. Additional blood samples for Pk will be taken using existing lines. Cognitive functioning will be assessed 30 days after hospitalisation.
The three dose levels to be given in this study are derived from effective dose levels in animal models that were neuroprotective after hypoxia-ischemia, both in newborn and in adult animals. In order to investigate whether 2-IB will also have a neuroprotective effect in adult patients after OHCA, clinical studies need to be performed. At present it is unknown whether these doses will also have a positive effect in human adults after OHCA.

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

* Admission to the ICU after OHCA and successful CPR due to a cardiac cause
* Duration of resuscitation no longer than 30 minutes
* Shockable rhythm as presenting rhythm
* Post anoxic coma on admission
* Ability to start study medication within 6 hours after cardiac arrest
* Age 18 years or older
* Eligible for treatment with a target temperature management of 36° C

Exclusion criteria

* No informed consent
* Known co-morbidity with a life expectancy of <6 months prior to cardiac arrest
* Women aged 49 or less
* Severe cognitive impairment (documented dementia) known prior to OHCA

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-05-2016
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	2-Iminobiotin
Generic name:	2-Iminobiotin

Ethics review

Approved WMO Date:	15-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	11-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2020
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-003902-17-NL
ClinicalTrials.gov	NCT02836340
CCMO	NL54915.018.15