TaPIR-Project

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON24118

Source
NTR

Brief title
TaPIR-Project

Health condition

sickle cell anemia, sikkelcelziekte, sikkelcelanemie, sikkel cel, thalassemia, thalassemie, unstable Hb, instabiel hb, haemoglobinopathies, haemoglobinopathie

Sponsors and support

Primary sponsor: Charles Kung, associate director Agios Pharmaceuticals
Source(s) of monetary or material Support: Agios pharmaceuticals

Intervention

Outcome measures

Primary outcome

Main objective:

- To investigate pyruvate kinase thermal stability in haemoglobinopathies.

Secondary outcome

Secondary objectives:

- To investigate the possibility of stimulation of PK activity and thermal stability in haemoglobinopathies by use of allosteric activators

- To investigate oxidative stress as a cause of decreased pyruvate kinase thermal stability in haemoglobinopathies

- To investigate the role of PK thermal stability related to clinical symptoms and disease severity

Study description

Background summary

Rationale:

Haemoglobinopathies encompass all genetic diseases of haemoglobin. Patients with haemoglobinopathies suffer from anaemia because of premature red blood cell destruction. The pathophysiology behind this is multifactorial and complex. However, increased oxidative stress is a common pathophysiologic feature that is shared by all haemoglobinopathies.

Pilot studies in our laboratory have shown that pyruvate kinase shows decreased stability in haemoglobinopathies. Since pyruvate kinase is essential for red blood cell energy supply and anti-oxidative defence we postulate that this instability could compromise red cell metabolism, and thereby, cellular survival. Also, by retrograde accumulation, loss of pyruvate kinase activity could lead to an increase in 2,3-DPG, which in turn is an important regulator of oxygen affinity of haemoglobin. Lowering 2,3-DPG levels is currently used as a therapeutic target in several clinical trials in sickle cell disease, a common form of haemoglobinopathy.

Currently, in our laboratory and clinic, pyruvate kinase-activators are tested that have been designed to treat the rare hereditary disease pyruvate kinase deficiency. Recently, the use of these allosteric activators has been extended to the field of thalassaemia, another common form of haemoglobinopathy. A study in a mouse model of thalassaemia showed successful stimulation of pyruvate kinase function resulting in increased haemoglobin levels in vivo. We therefore aim to further explore the role of decreased stability of PK in several forms of haemoglobinopathies in humans, and study the effect of restoring this instability by the use of allosteric activators ex vivo.

Objective:

Main objective:

- To investigate pyruvate kinase thermal stability in haemoglobinopathies.

Secondary objectives:

- To investigate the possibility of stimulation of PK activity and thermal stability by use of allosteric activators

- To investigate oxidative stress as a cause of decreased pyruvate kinase thermal stability in haemoglobinopathies

- To investigate the role of PK thermal stability related to clinical symptoms and disease severity

Study design: Case control study

Study population:

45 adult haemoglobinopathy patients, 15 hereditary anemia patients and 10 healthy controls.

Intervention (if applicable): not applicable

Main study parameters/endpoints:

Pyruvate kinase thermal stability, pyruvate kinase activity, 2,3-DPG/ATP, Emden Meyerhof pathway enzymes, reactive oxygen species, methaemoglobin

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients and healthy controls are asked for a single blood donation of 57 ml via venepuncture. Physical discomfort may include bruising. Also patients are asked permission for medical chart review.

Study objective

Observational study. We aim to investigate (thermal) stability of the enzyme pyruvate kinase in haemoglobinopathies. Secondary, we aim to investigate the possibility of stimulating the PK activity and stability ex vivo by use of allosteric activators. We aim to ibvestigate oxidative stress as a cause of decreased stability and we aim to investigate the role of PK thermal stability related to clinical symptoms and disease severity.

Study design

enrollment, end of study

Intervention

No intervention. This is an observational study

Contacts

Public
UMC Utrecht

HAS van Straaten
Utrecht
The Netherlands
Scientific
UMC Utrecht

HAS van Straaten
Utrecht
The Netherlands

Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Adult patients (18 years or older) with a diagnosis as listed above

- Participant is willing and able to give informed consent

Exclusion criteria

Exclusion criteria:

- Inability to give informed consent.

- Need for regular red blood cell transfusions (more than 8 transfusions a year)

- Recent transfusion, defined as within 2 months prior to enrolment).

The last two criteria do not lead to exclusion for patients with Unstable Hb, because of the extreme rarity of the diagnosis.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2017
Enrollment:	55
Type:	Anticipated

Ethics review

Not applicable

Application type:	Not applicable

Study registrations

Followed up by the following (possibly more current) registration

ID: 55777
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL6288
NTR-old	NTR6462
CCMO	NL59957.041.17
OMON	NL-OMON55777

Study results

Summary results
to be expected