Thermal stability of Pyruvate kinase In Red blood cells

Published: 10-08-2017
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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...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haemoglobinopathies
Study type	Observational invasive

Summary

ID

NL-OMON55777

Source
ToetsingOnline

Brief title
Tapir

Condition

- Haemoglobinopathies
- Blood and lymphatic system disorders congenital

Synonym
Haemoglobinopathies, hereditary anemia

Research involving
Human

Sponsors and support

Primary sponsor: Agios pharmaceuticals
Source(s) of monetary or material Support: Ministerie van OC&W,Agios pharmaceuticals

Intervention

Keyword: 2, 3-DPG, Pyruvate kinase, Sickle cell disease, Thalassemia

Outcome measures

Primary outcome

- To investigate pyruvate kinase thermal stability in haemoglobinopathies:

Parameters of interest are PK activity and thermal stability. Results obtained from patient cells will be compared with those from healthy controls, and between the different disease groups.

Secondary outcome

- Stimulation of PK in haemoglobinopathies by use of allosteric activators:

A comparison will be made between treated and untreated samples. Parameters of interest are glycolytic and pentose phosphate pathway intermediates, and biomarkers of oxidative stress.

- Oxidative stress as a cause of decreased PK thermal stability in haemoglobinopathies:

Conditions of severe oxidative stress will be mimicked by incubating red blood cells of both participants and healthy controls with oxidative agents with or without reducing compounds The endpoint is the difference in levels of glycolytic and pentose phosphate pathway intermediates and biomarkers of oxidative stress between oxidized and reduced samples.

- The role of PK thermal stability related to clinical symptoms and clinical disease severity:

Parameters of interest are incidence and prevalence of disease related organ

damage, transfusion burden, historical lab parameters and medication history

Study description

Background summary

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 PK 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.
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, a 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.

Study 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 burden and risks

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.

Contacts

Public
Agios pharmaceuticals

88 Sidney Street 88
Cambridge MA 02139
US
Scientific
Agios pharmaceuticals

88 Sidney Street 88
Cambridge MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Group 1: 20 Homozygous (HbSS) sickle cell patients or patients with compound heterozygosity for sickle cell disease and β-(0)-thalassemia. 10 patients with compound heterozygosity for sickle cell disease and hemoglobin C disease., Group 2: 20 β-thalassemia intermedia or major patients, Group 3: 5 unstable Hb

patients, Group 4: 15 other hereditary anemia patients, 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 12 transfusions a year)
- Recent transfusion, defined as within 1 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 invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-12-2017
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO

Date:	10-08-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 24118
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL59957.041.17