Assessment of endogenous oxalate production and investigation of glyoxylate/oxalate pathways in primary hyperoxaluria patients and healthy subjects

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Primary: Quantification of oxalate and glycine production in both healthy subjects and PH patients in order to obtain reference values for clinical trials.Secondary: To obtain more insight in the glyoxylate/oxalate pathway, and in particular the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON46913

Source
ToetsingOnline

Brief title
Oxalate production and metabolism in PH patients and healthy subjects

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism
- Urolithiases

Synonym
Primary hyperoxaluria type 1 and 2

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Dicerna Pharmaceuticals,Farmaceutische industrie

Intervention

Keyword: Metabolism, Oxalate, Stable Isotopes

Outcome measures

Primary outcome

Rate of appearance (Ra); oxalate.

Secondary outcome

Rate of appearance (Ra): glycolate and glycine.

[1-13C] and [U-13C] enrichment of glycine and oxalate.

Study description

Background summary

The Primary Hyperoxalurias are a group of rare inborn errors of glyoxylate metabolism characterized by an increased endogenous oxalate production, which leads to the development of urolithiasis, nephrocalcinosis and ultimately renal failure. Once PH patients develop renal failure systemic deposition of oxalate accelarates resulting in oxalosis, a life threatening condition affecting multiple organs most notably the skeleton, heart, bone marrow and skin.
To date, the only curative option is liver transplantation. This procedure however carries a high risk of morbidity and mortality and is limited given the sparsity of donors. Therefore, less invasive treatments are needed. Promising drugs based on RNA interference have recently been developed. One aims to inhibit the enzyme glyoxylate oxidase (GO), responsible for the production of the precursor of oxalate, the other aims to inhibit lactate dehydrogenasis (LDH); to reduce the production of oxalate in the liver. Previous studies with RNAi drugs have shown limited side effects.
In current practice, urinary oxalate excretion is used as the main outcome measure for studies in PH. However, the variability of urine oxalate excretion

in PH patients is large, limiting its validity as an outcome measure. Within this study we therefore aim to develop a more solid outcome measure, which is imperative in order to evaluate therapy efficacy of the new drugs in the upcoming phase III trials. Simultaneously, our aim is to obtain more insight into the complex metabolic pathways underlying PH1 and PH2.

Study objective

Primary: Quantification of oxalate and glycine production in both healthy subjects and PH patients in order to obtain reference values for clinical trials.

Secondary: To obtain more insight in the glyoxylate/oxalate pathway, and in particular the role of hydroxyproline, glycine and glycolate in endogenous oxalate production.

Study design

Experimental study

Intervention

(continuous primed) infusion with stable isotopes (identical for both groups): [U-13C]sodium-oxalate, [1-13C] Glycolate and [D5] Glycine

Study burden and risks

Subjects are asked to visit the AMC for one day (duration of visit is 10 hours). Subjects will have 2 intravenous cannula*s inserted, one for the administration of the stable isotopes and one for blood sampling. Subjects will be required to follow a diet low in oxalate for 3 days and start fasting 12 hours prior to the measurements.
A stable isotope is a naturally occurring atom whose nuclei contain the same number of protons but a different number of neutrons. This alters the mass of the atom but not its chemical nature. In contrast to radioactive isotopes, there is no spontaneous decay of stable isotopes (hence the name stable isotopes). There are no reported risks that can be attributed to the experimental use of stable isotopes in humans.

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

PH patient:
- A diagnosis of Primary Hyperoxaluria type 1 (PH1) or Primary Hyperoxaluria type 2 (PH2) as assessed by DNA mutational analysis
- Age 18 * 65 years;Healthy volunteer:
- Age 18 * 65 years
- eGFR > 80 ml/min · 1.73 m2 (Cockroft-Gault)

Exclusion criteria

- Acute or chronic disease (other than PH), that would interfere with the subject's safety and ability to comply with protocol requirements.
- Pregnancy or lactation at the time of screening or enrollment
- Any disorder or alteration in mental status that would preclude understanding of the informed consent process and/or completion of the study related evaluations.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-09-2017
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO Date:	29-06-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-09-2019
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
CCMO	NL54838.018.15