The reliability of the 13C-phenylalanine breath test for phenylketonuria patients: a pilot study

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To establish the test-retest reliability of the 13C-PBT for measuring Phe hydroxylation in patients with PKU.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON52773

Source
ToetsingOnline

Brief title
The 13C-phenylalanine breath test in PKU

Condition

- Metabolic and nutritional disorders congenital

Synonym
Phenylalanine hydroxylase deficiency; phenylketonuria; PKU.

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting vrienden Beatrix Kinderziekenhuis;Nederlandse PKU Vereniging

Intervention

Keyword: Breath test, Phenylketonuria, Reliability

Outcome measures

Primary outcome

The test-retest reliability of the 13C-PBT for measuring Phe hydroxylation,

expressed as the intraclass correlation coefficient (ICC).

Secondary outcome

- The relationship between Phe hydroxylation as measured by the 13C-PBT and the

genotypic phenotype values (GPV), as a measure of disease severity.

- A description (mean with 95% confidence interval) of the outcomes of the

13C-PBT in healthy persons.

Study description

Background summary

Phenylketonuria (PKU) is an inborn error of amino acid metabolism that affects the hydroxylation of phenylalanine (Phe). To avoid severe neurological complications associated with high blood Phe concentrations, it is necessary to follow a lifelong treatment focused on keeping blood phenylalanine concentrations within target range. While a dietary intervention that limits Phe intake has been the mainstay of treatment for the last decades, recent and upcoming treatment options are focussing on improving the patient*s capability to metabolize Phe. These new treatments include cofactor treatment with tetrahydrobiopterin and sepiapterin, but also therapeutic liver repopulation and gene therapy. Assessing the effectiveness of such treatments is important for research and patient care, and can, in theory, relatively easily be done using a 13C-Phe breath test (13C-PBT). This test is based on quantifying the conversion of 13C-Phe into 13C-Tyr by measuring 13CO2 in breath samples. While this method has been described several times in the literature, no research has yet focused on examining the test-retest reliability of the 13C-PBT in PKU patients under stable conditions (e.g. without intervention), although this is vital for evaluating the effect of a certain treatment using this test.

Study objective

To establish the test-retest reliability of the 13C-PBT for measuring Phe hydroxylation in patients with PKU.

Study design

This is an observational study consisting of three parts:
- Part A: healthy volunteers > 16 years will undergo the 13C-PBT to optimize the protocol for part B.
- Part B: PKU patients > 16 years will undergo the 13C-PBT twice to establish the within-subject variation of Phe hydroxylation as measured by the 13C-PBT.
- Part C: PKU patients < 16 years will undergo the 13C-PBT twice to establish the within-subject variation of Phe hydroxylation as measured by the 13C-PBT. Part C will only take place in case analyses from part B suggest that the test-retest reliability is at least moderate (defined as an intraclass correlation coefficient > 0.40).

Study burden and risks

We assess that the burden of this study is low and the risks are minimal. Participants in study part A will visit the UMCG once and will undergo the 13C-PBT once as well. Participants in study part B and C will visit the UMCG twice, will undergo the 13C-PBT twice, will make six bloodspots, and will give three samples of blood in total. Furthermore, participant in part B and C will be instructed to make a dietary adjustment on the day of the 13C-PBT and to make a blood spot on the following day. Since this is not a therapeutic study, there are no direct benefits for the participants. There are however potential benefits from the information gained from this study, as this study will be essential for using the 13C-PBT to determine the effect of different (future) treatment options in individual patients with PKU. Because we expect that the 13C-PBT will also be relevant for the care of children with PKU, it is necessary to also include patients < 16 years to investigate and confirm our outcomes in this age category.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

Part A (healthy adult volunteers)
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- At least 16 years old.

Part B (adults with PKU)
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- At least 16 years old.
- Diagnosed with PKU.
- Known genetic mutation of the PAH gene.
- Not receiving pharmacological treatment with BH4.
- Able to comply with the study protocol as assessed by their treating physician (e.g. being able to comply with fasting overnight and remain rested during the 13C-PBT).
- For females: a regular menstrual cycle (of approximately 4 weeks) OR post-menopausal.

To be able to reach our secondary objective, it is necessary to include patients with different phenotypes. Phenotypes of PKU patients can be expressed

by their genotypic phenotype values (GPV), which is a numerical representation of PAH activity (and thus disease severity) that depends on the genotype of the patient. An online database (http://www.biopku.org) provides GPVs for almost all different genotypes (15). Of the 20 patients to be included in part B, we aim to include >= 5 patients with classic PKU (GPV: 0-2.7), >= 5 patients with mild PKU (GPV: 2.8-6.6), and >= 5 patients with mild hyperphenylalaninemia (GPV: 6.7-10.0).

Part C (children with PKU)
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- >= 6 years and <16 years old.
- Diagnosed with PKU.
- Known genetic mutation of the PAH gene.
- Not receiving pharmacological treatment with BH4.
- Able to comply with the study protocol as assessed by their treating physician (e.g. being able to comply with fasting overnight and remain rested during the 13C-PBT).
- For females: a regular menstrual cycle (of approximately 4 weeks) OR pre-menarchic.

Similar to part B, we aim to include >= 5 patients with classic PKU (GPV: 0-2.7), >= 5 patients with mild PKU (GPV: 2.8-6.6), and >= 5 patients with mild hyperphenylalaninemia (GPV: 6.7-10.0).

Exclusion criteria

Part A, B and C
A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Pregnancy or wishing to become pregnant.
- Known liver and/or kidney dysfunction.
- Use of medication that may influence liver and/or kidney function.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-05-2024
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	24-11-2023
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Not approved

Date:	23-12-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL71868.042.20