Residual galactose oxidation capacity and galactosylation abnormalities as possible predictors for galactose tolerance and outcome in patients with galactose-1-phosphate uridyltransferase deficiency

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The objective of this study is to investigate the association of the residual galactose oxidation capacity (measured in vivo and in vitro) and of galactosylation abnormalities with outcome in patients with galactosemia.

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

Summary

ID

NL-OMON46279

Source
ToetsingOnline

Brief title
Galactose oxidation and galactosylation in Classical Galactosemia

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism

Synonym
Classical galactosemia, galactose-1-phosphate uridyltransferase deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Stichting Metakids

Intervention

Keyword: classical galactosemia, fibroblast, galactosylation, oxidation

Outcome measures

Primary outcome

Main study parameters/endpoints:

Part A: Galactosylation patterns

In serum G0 (agalactosylated)/G1 (monogalactosylated) and G0/G2 (digalactosylated) incorporation ratios which signal N glycan processing defects will be determined. The association of these incorporation ratios with phenotype of CG (mild or severe) will be assessed.

Part B1: In vivo galactose oxidation capacity

The cumulative percentage of ingested [1-13C galactose] retrieved as [1-13C] CO2 in expired air (CUMPD), will be measured in breath samples taken at baseline and at 60, 90 and 120 minutes after a dose of 7 mg/kg [1-13C] galactose. The association of these cumulative retrieved proportions with phenotype of CG (mild or severe) will be assessed.

Part B2: In vitro galactose oxidation capacity

The galactose index (ratio of U13C6-Galactose-1-phosphate/ U13C6-UDP-Galactose) which is a measure for galactose metabolism, will be measured in fibroblasts after two hours of incubation with U13C6-galactose.The association of this galactose index with phenotype of CG (mild or severe) will be assessed.

Group means will be compared, we will perform logistic regression analysis to quantify the association between determinants and phenotype subgroup. Receiver Operator Characteristics (ROC) curves will be made, and the Area Under the Curve (AUC) will be calculated to determine the usefulness of the determinants as diagnostic indicators for severe phenotype.

Secondary outcome

NA

Study description

Background summary

Classical galactosemia (CG) is an inborn error of galactose metabolism, caused by a profound deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT). Infants with CG develop a life-threatening disease in the first week of life after ingestion of galactose from breastmilk or infant formula. The only available treatment is a life-long galactose restricted diet. Although this dietary treatment is life-saving in the newborn period, it does not prevent long-term complications such as cognitive impairment, neurological complications, and ovarian failure in females. The advised restriction of galactose varies worldwide, but most patients have a severely restricted diet. The clinical outcome spectrum of CG is highly heterogeneous, with patient IQs varying from 44 to 120, which is poorly understood, and valid prognostic biomarkers are lacking.

Furthermore, since introduction of CG into the Dutch newborn screening program in 2007, individuals are identified with previously unknown clinical and biochemical phenotypes and genotypes. Therefore, outcome of individual patients

cannot be predicted. Currently, all individuals with GALT activity <15% are treated. Recently, it was demonstrated that galactose over-restriction may cause galactosylation abnormalities comparable to galactose intoxication. Thus, the strict diet may well be harmful to some. There is an urgent need for individualized prognostication and treatment.

We hypothesize that the long-term complications in CG are caused by defective galactosylation of proteins and lipids. We propose that galactosylation abnormalities in CG are modified by individual residual galactose oxidation capacity. Measurement of residual galactose oxidation capacity and evaluation of galactosylation abnormalities may ultimately enable us to predict dietary galactose tolerance and outcome.

Study objective

The objective of this study is to investigate the association of the residual galactose oxidation capacity (measured in vivo and in vitro) and of galactosylation abnormalities with outcome in patients with galactosemia.

Study design

Patients with GALT activity <15% who are currently treated for CG will be categorized in two subgroups: severe phenotype, or mild phenotype, based on intelligence/developmental quotient and educational outcome.

Part A: Galactosylation abnormalities in serum (taken previously and stored in biobank) will be measured in all patients.
Part B: Residual galactose oxidation capacity will be determined with two methods:
B1: In vivo measurement (galactose breath test, in both children and adult patients)
B2: In vitro galactose oxidation in fibroblasts (skin biopsy will only be performed in competent adults).

Intervention

Part B1:
In vivo galactose oxidation measurement (galactose breath test)
The subject is not allowed to eat or drink 2 hours before the test. Drinking water is allowed during the test. Adults will be resting in a chair and can watch television or use their computer. Children may also walk around but must avoid running and exercise. An oral dose of 7 mg/kg [1-13C] galactose will be given to each patient once as an aqueous solution. Breath samples will be taken after 60,90 and 120 minutes by collecting air exhaled into a vacuum tube.

Part B2:

A skin biopsy for in vitro galactose oxidation in fibroblasts will be performed in competent adults only. If fibroblasts of patients are already available, as they were sampled as part of patient care, they will be used in this part of the study if patient/parents have given written informed consent.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

The risks associated with participation in any part of this study can be considered negligible.

Part A: No risk. Serum samples which have been previously collected in the Biobank Stofwisselingsziekten will be used.

Part B1: Negligible because it concerns administration of a stable isotope by mouth. A dose of 7 mg/kg is a safe dose in CG, as it is far below the body*s daily endogenous production of galactose. There are no known risks of oral administration of [1-13C] galactose, other than small risk of aspiration. The burden can be considered minimal, because 1) no invasive procedures will be performed, 2) effort needed from patients is small since they only need to drink the in water dissolved [1-13C] galactose and breathe in a tube three times if possible, 3) patients can rest and watch television or play on their computer if they want, 4) a relatively small amount of time has to be invested (procedures are performed once).

Part B2: Negligible, because a skin biopsy is a generally safe procedure, but complications can occur, including bleeding, bruising, scarring, and infection. The burden of the procedure is considered minimal for competent adults, as the procedure is performed while the skin in anesthetized, the procedure is very brief, and it is performed only once.

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)
Elderly (65 years and older)

Inclusion criteria

GALT enzyme activity <15% of healthy controls and/or
two null or severe missence variations in the GALT gene

Exclusion criteria

individuals with swallowing difficulties will be excluded from part B1 (galactose breath test) of the study

Study design

Design

Study type:	Observational invasive
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):	14-09-2017
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	10-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2018
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	NL61575.018.17