The effect of lactate administration on cerebral blood flow during hypoglycemia

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To investigate the effect of intravenous lactate administration, compared to placebo, on thalamic (regional) and global CBF during euglycemia and hypoglycemia in patients with T1DM and NAH.

Ethical review	Approved WMO
Status	Completed
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Interventional

Summary

ID

NL-OMON48795

Source
ToetsingOnline

Brief title
The effect of lactate administration on cerebral blood flow

Condition

- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: The European Foundation for the study of Diabetes

Intervention

Keyword: awareness of hypoglycemia, CBF, lactate, T1DM

Outcome measures

Primary outcome

The change in regional thalamic CBF in response to intravenous lactate infusion compared to placebo, during hypoglycemia

Secondary outcome

- Change in global CBF in response to intravenous lactate infusion compared to placebo, during hypoglycemia
- Change in plasma levels of counterregulatory hormones in response to hypoglycemia and euglycemia with and without lactate infusion (adrenaline, noradrenaline, growth hormone and cortisol)
- Change in hypoglycemic symptoms scores in response to hypoglycemia with and without lactate infusion

Study description

Background summary

It is thought that altered brain lactate handling is involved in the development of impaired awareness of hypoglycemia (IAH), i.e. the inability to timely detect hypoglycemia in people with type 1 diabetes (T1DM). Infusion of lactate diminishes symptomatic and hormonal responses to hypoglycemia in patients with normal awareness of hypolgycemia (NAH), resembling the situation of patients with IAH. It is unknown whether this attenuating effect is due to brain lactate oxidation or the result of lactate-induced alterations of global and regional cerebral blood flow (CBF).

Normally, hypoglycemia causes a redistribution of CBF towards the thalamus, from where the sympathetic response to hypoglycemia is coordinated, but in IAH this effect is absent and global CBF is increased. We hypothesize that lactate

infusion in patients with NAH will result in blunting of thalamic activation and/or enhanced global CBF. If so, these results may help delineating the pathogenesis of IAH which eventually creates new avenues to protect against the morbidity associated with hypoglycemia and IAH.

Study objective

To investigate the effect of intravenous lactate administration, compared to placebo, on thalamic (regional) and global CBF during euglycemia and hypoglycemia in patients with T1DM and NAH.

Study design

Single-blind placebo controlled, randomized cross-over intervention study

Intervention

On two separate occasions, patients with T1DM and NAH will undergo a hyperinsulinemic euglycemic-hypoglycemic glucose clamp with or without the infusion of exogenous lactate. ASL-MRI will be applied to measure global and regional changes in CBF.

Study burden and risks

The hypoglycemic condition is likely to induce typical symptoms (e.g. sweating, feeling hungry, palpitations) in T1DM patients with NAH, but is usually well-tolerated and less pronounced when lactate is infused. The risk for more severe hypoglycemia is negligible. The use of venous and arterial catheters may lead to hematomas and/or phlebitis, yet this is self-limiting and has in our hands never led to permanent damage. ASL-MRI is a non-invasive method to determine CBF, involving high magnetic fields, which are not associated with adverse events other than possible claustrophobia due to lying in the small MR-bore.

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

- Diabetes duration * 1 year
- Age: 18-50 years
- Body-Mass Index: 18-30 kg/m2
- HbA1c: <75 mmol/mol (<9%)
- Outcome Clarke questionnaire: 0-1
- Blood pressure: <160/90 mmHg

Exclusion criteria

- Inability to provide informed consent
- Use medication other than insulin, except for oral contraceptives or stable thyroxin supplementation therapy
- Presence of any other medical condition that might interfere with the study protocol, such as brain injuries, epilepsy, a major cardiovascular disease event or cardiac failure, known liver disease, anxiety disorders or a history of panic attacks.
- Microvascular complications of T1DM
- MRI contraindications (pregnancy, severe claustrophobia, metal parts in body)

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-06-2018
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	08-03-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-03-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-02-2019

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
EudraCT	EUCTR2018-000684-82-NL
CCMO	NL64421.091.18
Other	nog niet bekend

Study results

Date completed:	14-05-2019
Results posted:	25-11-2020

First publication
25-11-2020