Use of Copeptin Measurement after Arginine Infusion for the Diagnosis of Diabetes Insipidus - the CARGOx Study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON48431

Source
ToetsingOnline

Brief title
CARGOx

Condition

- Hypothalamus and pituitary gland disorders

Synonym
diabetes insipidus, polyuria-polydipsia syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Prof. Mirjam Christ-Crain, University Hospital Basel (USB)

Source(s) of monetary or material Support: Ministerie van OC&W,Swiss National Science Foundation;University Hospital Basel Zwitserland

Intervention

Keyword: copeptin, diabetes insipidus, polyuria-polydipsia syndrome, primary polydipsia

Outcome measures

Primary outcome

The primary outcome is the overall diagnostic accuracy - defined as the proportion of correct diagnoses - of each diagnostic procedure in differentiating patients with central diabetes insipidus (cDI) from patients with primary polydipsia (PP).

Copeptin measurement after arginine-stimulation (CAS) will be compared for non-inferiority to the current best diagnostic test copeptin measurement after hypertonic saline infusion (HIS).

Secondary outcome

- Sensitivity, specificity, positive and negative predictive value of both diagnostic procedures for each diagnosis (PP, partial and complete DI) according to recommended diagnostic test criteria and previously generated cutoff values

- best fit diagnostic copeptin cut-off values for differentiation between each diagnosis (PP, partial and complete DI) upon arginine stimulation (CAS) and hypertonic saline infusion stimulation (HIS)

- Accuracy, sensitivity and specificity of the copeptin cut-off of 3.8 pmol/l after 60 minutes and 4.1 pmol/l after 90 minutes for CAS.

- Accuracy, sensitivity and specificity of the copeptin cut-off of 6.5pmol/l

for HIS.

- frequency and severity of thirst, headache, nausea, vertigo and general

malaise, assessed by visual analogue scale (VAS) during CAS and HIS

- subjective burden assessed by visual analogue scale (VAS) of the CAS and HIS

method

- frequency of test preference according to evaluation at follow up visit

(choice between: CAS preferred / HIS preferred / no preference)

- Health care costs of CAS and HIS

Study description

Background summary

The differential diagnosis of central diabetes insipidus (cDI) is difficult and the current test with the highest diagnostic accuracy is copeptin measurement after hypertonic saline infusion (HIS). Although the HIS improved diagnostic accuracy compared to the standard water deprivation test used for decades before, it still comprises discomfort for patients due to the rise in plasma sodium levels above 149mmol/l and requires the presence of medical staff at all times for controls of plasma sodium levels.
The arginine stimulation test is routinely used to stimulate growth hormone. Own data in 96 patients with polyuria / polydipsia syndrome showed that arginine infusion is a potent stimulator of the neurohypophysis and provides a new diagnostic tool in the differential diagnosis of cDI. Copeptin measurements upon arginine stimulation (CAS) discriminated patients with diabetes insipidus vs. patients with primary polydipsia with a high diagnostic accuracy of 93% and the infusion is generally well tolerated.
To validate these results and to compare them against the HIS a large multicenter trial is needed, where the diagnostic accuracy of the CAS is compared to the HIS.

Study objective

The primary objective of this prospective international multicenter diagnostic study is the comparison of the diagnostic accuracy between copeptin measurement after arginine-stimulation (CAS) and the current best diagnostic test copeptin measurement after hypertonic saline infusion (HIS) in the differential

diagnosis of diabetes insipidus

Study design

diagnostic study

Intervention

A) Arginine infusion test
Intravenous infusion of 0.5 g / kg body weight (max. 40 g) L-Arginine Hydrochlorid (21%) diluted in 500 ml NaCl 0.9% is administered for 30 minutes. Blood samples for later copeptin measurement are collected before, 60 and 90 minutes after the start of the infusion

B) 3% NaCl infusion test
Intravenous infusion of NaCl 3% is first given as a bolus of 250 ml for 15 minutes, then with an infusion rate of 0.15 ml per kg body weight per minute until the sodium content in plasma has risen to> 149 mmol / l. Plasma copeptin is measured at this point. Once the measurement is complete, patients should drink at least 30 ml / kg body weight within 60 minutes while simultaneously administering 5% 500 ml glucose to ensure that plasma sodium levels fall within the normal range.

Study burden and risks

The infusion with arginine is also used in children and adults to stimulate growth hormone and has no relevant side effects. Rarely, nausea and a low level of discomfort have been reported during the infusion.

The most common symptoms during the 3% NaCl infusion test were thirst, moderate headache, and moderate malaise. All symptoms are to be expected due to hypertonic stimulation and immediately improved after discontinuation of the infusion.

According to the information provided above, we consider the risk of this diagnostic test to be small. For safety reasons, patients with epilepsy, uncontrolled arterial hypertension, heart failure, cirrhosis of the liver or unadjusted adrenal or thyroid deficiency are excluded from participation.

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

1. Age >= 18 years
2. Hypotonic polyuria / polydipsia syndrome defined as:
• polyuria >50ml/kg body weight/24h and polydipsia >3l /24h or known diabetes insipidus under treatment with DDAVP
• Urine-Osmolality <800mOsm/L

Exclusion criteria

1. Polyuria / polydipsia secondary to diabetes mellitus, hypercalcemia or hypokalemia
2. Nephrogenic diabetes insipidus (defined as baseline copeptin level >21.4pmol/L)
3. Evidence of any acute illness
4. Epilepsy requiring treatment
5. Uncontrolled arterial hypertension (blood pressure >160/100mmHg at baseline)
6. Cardiac failure (NYHA III-IV)
7. Liver cirrhosis (Child B-C)

8. Uncorrected adrenal or thyroidal deficiency
9. Patients refusing or unable to give written informed consent
10. Pregnancy or breast feeding
11. End of life care

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-06-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	L-Arginin-Hydrochlorid 21% Braun
Generic name:	L-Arginin-Hydrochlorid 21%
Product type:	Medicine
Brand name:	Sodium Chloride 3% injection solution Baxter Healthcare Corporation
Generic name:	Natriumchloride 30 g/L (3%)

Ethics review

Approved WMO

Date:	15-10-2019

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2018-004159-19-NL
ClinicalTrials.gov	NCT03572166
CCMO	NL69582.078.19