Stimulation of ADH independent urine concentration in healthy volunteers

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are sildenafil, metformin and simvastatin effective in stimulation of ADH independent urine concentration in man?

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON45483

Source
ToetsingOnline

Brief title
ADH independent urine concentration in healthy volunteers

Condition

- Nephropathies

Synonym
diabetes insipidus, nephrogenic diabetes insipidus

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: subsidie college zorgverzekeringen

Intervention

Keyword: ADH, urine concentration

Outcome measures

Primary outcome

minimal urine osmolalility after water loading

Secondary outcome

serum sodium, blood pressure, side effects, urine volume within 4 hours after

water loading

Study description

Background summary

Nephrogenic diabetes insipidus (NDI) is a rare disorder characterized by resistance of the kidney tubules to the action of the anti-diuretic hormone ADH, resulting in a decrease in the capacity of the kidney to concentrate urine. Water reabsorption in the collecting duct is initiated by ADH that binds to its receptor (type 2 vasopressin receptor, V2R) in collecting duct principal cells, which activates intracellular processes such as adenylyl cyclase. This causes the insertion of water channels (AQP2) into the apical membrane through which water can enter the cell. The most common cause of hereditary NDI are mutations of the V2R and the most common cause of acquired NDI is chronic lithium therapy which reduces adenylyl cyclase activity. The inability to concentrate the urine results in high urine volumes, which can be as high as 15 liters a day. This cab lead to several secondary problems, such as hypernatremia and rapid dehydration when water intake is restricted. Current treatment consists of drinking large amounts of water and attempts to lower the urine output by a low-salt and low protein diet, diuretics (inducing hypovolemia-induced proximal sodium and water re-absorption) and the use of anti-inflammatory drugs. These measures however are only partly able to correct the polyuria. NDI therefore is a chronic disease affecting the quality of life. Recent reports have suggested novel therapeutic possibilities that could be more effective than the current standard of care.

The first potential drug is sildenafil. Sildenafil increases cyclic GMP which is thought to induce phosphorylation of AQP2. Sildenafil indeed increased the apical accumulation of AQP2 in rats with central diabetes insipidus [Bouley 2005, Sanches 2012]. Assadi described a child with a mutation in V2R who showed a greater decrease in urine volume and a greater increase in urine osmolality after 10 days treatment with sildenafil compared to conventional treatment with hydrochlorothiazide, amiloride and indomethacin [Assadi 2015].

The second potential drug is metformin. Metformin activates adenosine monophosphate kinase (AMPK), which increases phopshorylation and accumulation of AQP2 resulting in an increase of urine osmolality in rats and mice [Klein 2016, Efe 2016]. The effect of metformin was maintained for 10 days in tolvaptan treated rats (a model for nephrogenic diabetes insipidus) [Efe, 2016].

The third potential drug is simvastatin. Simvastatin is thought to enhance the expression of AQP2 through downregulation of Rho GTPase activation and the inhibition of endocytosis [Li 2011]. In line with this finding it was shown that patients treated with simvastatin show an increase in urinary AQP2 and increase in urine osmolality [Procino, 2016].

These three drugs thus might have an ADH independent effect on AQP2 and water transport in the collecting duct and could thereby serve as a treatment option of patients with NDI.

Study objective

are sildenafil, metformin and simvastatin effective in stimulation of ADH independent urine concentration in man?

Study design

This is a prospective intervention study in which healthy volunteers will receive sildenafil, metformin or simvastatin during one week. At a baseline moment and at the end of the week we will perform a water loading test which will suppress ADH.

Intervention

use of sildenafil, metformin or simvastatin

Study burden and risks

Healthy volunteers will only have a small risk for small harm.

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

age >18 years old

Exclusion criteria

* any medical history, kidney damage
* inability to give informed consent
* pregnancy
* medication use

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-04-2017
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Metformin
Generic name:	Metformin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sildenafil
Generic name:	Sildenafil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Simvastatin
Generic name:	Simvastatin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-01-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-03-2017
Application type:	First submission
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	EUCTR2016-004943-35-NL
CCMO	NL60170.091.16