Effect of N-acetylcysteine on hydrogen sulfide in chronic kidney disease

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Primary Objective: Our primary objective is to investigate the effect of NAC on H2S levels in plasma in different patient groups, i.e. healthy volunteers, CKD patients, and dialysis patients. We hypothesize that there is an increase in H2S levels...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON36609

Source
ToetsingOnline

Brief title
Effect of NAC on H2S in CKD

Condition

- Renal disorders (excl nephropathies)

Synonym
chronic kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Nierstichting

Intervention

Keyword: chronic kidney disease, H2S, hydrogen sulfide, N-acetylcysteine

Outcome measures

Primary outcome

H2S levels in plasma.

Secondary outcome

Oxidative stress markers:

- thiobarbituric acid reactive substances (TBARS)

- superoxide dismutase (SOD)

- glutathione peroxidase (GPx)

- oxidized low-density lipoprotein (ox-LDL)

Inflammation markers:

- high-sensitivity C-reactive protein (hs-CRP)

- interleukin-6 (IL-6)

- connective tissue growth factor (CTGF)

Endothelial cell markers:

- intracellular adhesion molecule 1 (ICAM-1)

- E-selectin

- vascular cell adhesion molecule 1 (VCAM-1)

Study description

Background summary

The incidence of cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD) is high (Go, NEJM 2004).This is partly explained by the so called traditional risk factors, like hypertension, diabetes mellitus, and dyslipidemia, but risk factors specific to CKD also contribute to this high incidence. Nitric oxide (NO) deficiency, oxidative stress, endothelial dysfunction, and inflammation are considered to be such factors.

NO deficiency has a crucial role in progression of CKD
NO is an important player in the maintenance of target organ health (e.g. kidney and heart) and blood pressure. Patients with CKD generally show reduced NO production, reduced NO bioavailability and disturbed redox balance (Baylis, Am J Physiol Renal Physiol 2008; Kao, J Hum Hypertension 2010). Total NO production is decreased due to impaired endothelial and renal production of NO. With less NO, endothelial dysfunction, hypertension, and inflammation occur. Indeed, NO depletion caused systemic and glomerular hypertension, glomerular ischemia, glomerulosclerosis, tubulointerstitial injury, and proteinuria (Zatz, Hypertension 1998, Verhagen, KI 1999, Attia, JASN 2001). It is therefore likely that CKD-induced NO deficiency contributes to progression of renal damage. Thus, increasing NO, improving endothelial function, and reducing oxidative stress and inflammation, are obvious therapeutic targets.

H2S as backup mechanism for NO deficiency in CKD
Previous studies done by our group suggest renal hydrogen sulfide (H2S) and carbon monoxide (CO) production to be involved during chronic NO depletion (Attia, JASN 2001; Wesseling, Physiol Genomics 2007). Interestingly, these two gaseous molecules share the same signaling and vasorelaxant properties as NO, providing backup for each other in the vascular system (Wang, FASEB J 2002). H2S is mainly produced by conversion of L-cysteine by cystathionine β-synthase (CBS) or by g-cystathionase (CTH) and CO is mainly produced by heme oxygenase-1 via degradation of a heme (HO-1) (Li, Amino Acids 2009).
Although there are drugs that enhance CO and NO availability in rodents, none of them can be applied in humans. Therefore, the focus of our research is on the potential role of H2S in the protection of the kidneys in patients with CKD.

Until now, the backup system of NO by H2S is poorly defined. Recently, GFR was shown to partly depend on H2S blood levels. Renal damage was associated with diminished H2S levels and this was ameliorated when the H2S level was enhanced (Xia, J Pharmacol Exp Therap 2009). H2S production may be reduced as renal function becomes impaired. Indeed, plasma H2S levels were found to be significantly reduced in hemodialysis patients (Perna, NDT 2009). Whether this also occurs in patients with CKD, not on dialysis, is unknown.

N-acetylcysteine (NAC) to enhance H2S availability in humans

The readily available drug NAC is used in clinical medicine as a mucolytic agent, as an antidote for acetaminophen overdose, and in preventing contrast-induced nephropathy (see also Chapter 6). It is inexpensive, safe, and well tolerated by patients and could be applied to humans to enhance renal and systemic H2S. NAC is rapidly absorbed and easily converted to L-cysteine. L-cysteine is the main substrate for H2S production (and glutathione and taurine). Therefore, NAC should enable us to stimulate H2S production in humans. The potential benefits of NAC in CKD were shown in a randomized, placebo-controlled trial in which hemodialysis patients were treated with NAC 600 mg BID. Treatment with NAC reduced the composite cardiovascular end points (Tepel, Circulation 2003).

In the proposed study we wish to investigate the effect of NAC on H2S levels.

Study objective

Primary Objective:
Our primary objective is to investigate the effect of NAC on H2S levels in plasma in different patient groups, i.e. healthy volunteers, CKD patients, and dialysis patients. We hypothesize that there is an increase in H2S levels after treatment with NAC.

Secondary Objective:
Our secondary objective is to investigate differences in plasma H2S levels between healthy volunteers, CKD patients, and dialysis patients and between males and females. We hypothesize that there is a reduction in H2S production when renal function becomes impaired. Furthermore, we will investigate the effect of NAC on markers of oxidative stress, inflammation, and endothelial dysfunction.

Study design

Study Type: Interventional

Study Design: Allocation: Non-Randomized
Control: Uncontrolled
Endpoint Classification: Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Study Duration: 48 hours

Intervention

All study participants will receive 4 gifts of N-acetylcysteine 600 mg BID.

Study burden and risks

For this study we need one extra blood collection before NAC treatment and one blood collection after NAC treatment. NAC in the oral form is safe and well tolerated.

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

Healthy volunteers:
- Adult (> 18 years and older)
- Healthy, as assessed by medical history, blood pressure, plasma creatinine, and urine dipstick

- No medication use, non-smoking

CKD patient:
- Adult (> 18 years and older)
- CKD stage 3-4 (GFR 15-60 ml/min);Hemodialysis patient:
- Adult (> 18 years and older)
- Hemodialysis patient;Peritoneal dialysis patients
- Adult (> 18 years and older)
- Peritoneal dialysis patient

Exclusion criteria

Unable to give informed consent
Hypersensitivity to N-acetylcysteine
Pregnancy
Untreated peptic ulcus

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-07-2011
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	N-acetylcysteine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	29-11-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-06-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2010-022994-32-NL
ClinicalTrials.gov	NCT01232257
CCMO	NL34009.041.10