N-Acetylcysteine In The Treatment of Sickle Cell Disease

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23090

Source
NTR

Brief title
NAC in SCD

Health condition

sickle cell disease (anemia), hypoxia-reperfusion injury, endothelial damage, oxidative stress, NO-availability, inflammation, sikkelcelziekte, chronische ontsteking, endotheelschade.

Sponsors and support

Primary sponsor: This project will be carried out by the CURAMA programme, which is a collaborative effort between the Department of Vascular Medicine, Academic Medical Center (Amsterdam, the Netherlands), the Department of Internal Medicine Slotervaart Hospital (Amsterdam, the Netherlands), the Department of Internal Medicine, Sint Elisabeth Hospital (Curaçao, Netherlands Antilles), Red Cross Bloodbank Foundation Curaçao (Curaçao, Netherlands Antilles), the Laboratory of Clinical Thrombosis and Hemostasis in the Department of Internal Medicine, Academic Hospital Maatsricht (Maastricht, the Netherlands), the Department of Clinical Chemistry (Groningen, the Netherlands) and the department of Hematology, Erasmus Medical Center (Rotterdam, the Netherlands). CURAMA is embedded in the Antillean Institute of Health Research.
Source(s) of monetary or material Support: fund = initiator = sponsor

Intervention

Outcome measures

Primary outcome

Primary end-points are the effects of NAC on the laboratory markers (hemoglobin, red blood cell counts, reticulocyte counts, leukocyte counts and differentiation, platelet counts, erythrocyte sedimentation rate, a blood smear will be analyzed microscopically for the number of ISC per field, as well as the number of Heinz bodies, intra-erythrocytic GSH and GSSG levels, NO availability, SRBC phosphatidylserine (PS) exposure, annexin V, creatinine, BUN, electrolytes, transaminase levels, albumin levels, LDH, indirect bilirubin levels, free hemoglobin levels, high sensitive CRP, sVCAM-1, ET-1, IL-8, pro-thrombin fragments (F1.2), D-dimer levels, protein S (free and total) and C activity, vWF-Ag activity).

Secondary outcome

Tolerability of study medication (in this phase admittedly in a non-controlled fashion) at every visit by history taking and by scoring of a NAC for SCD check-list.

Study description

Background summary

The pathophysiology of sickle cell vasoocclusion is of a complex nature. It is now clear that, next to erythrocyte rigidity, the pathophysiology of sickle cell vasoocclusion involves cytokines, adhesion molecules, thrombus formation, platelet-, leukocyte- and endothelial activation, reactive oxygen species (ROS). Thus, it seems that in vivo, a complex interplay between many biological factors determine the extent to which vasoocclusion occurs in a given patient.
Gluthation (GSH), an amino-thiol (a thiol is a molecule with a SH group) is the most abundant antioxidant in our body and is a crucial defense against free radicals. Our body is equipped with a vast array of antioxidant substances for protection against oxidative stressors in health (varying from sun-light exposure to tobacco smoking) and disease (atherosclerosis, sepsis). NAC is highly permeable to cell membranes and within the cytoplasm it is converted to L-cysteine, which is a precursor to GSH. It is well known as a mucolytic agent and for treatment of acetaminophen induced liver toxicity. NAC has been investigated for treatment of many disease states, such as cardiovascular disease, human immunodeficiency virus infections, sepsis and acute respiratory distress syndrome. NAC is an important antioxidant with pleiotropic effects on inflammation and vasomotor function. Reactive oxygen species (ROS) may play a central role in the pathophysiology of SCD related vascular occlusion and organ damage, and NAC administration to patients with SCD may be of benefit via several mechanisms as detailed below.

Objectives:
To determine whether NAC therapy results in decreased red cell PS exposure, endothelial activation, inflammation, and reduction in clotting activation in the steady state.

Study objective

We hypothesize that treatment of sickle cell patients with NAC results in reduced red cell PS exposure, reduced endothelial activation, increased NO availability, reduced coagulation activation and reduced inflammation detectable with specific laboratory testing, as well as a reduction of ISC's and Heinz Body formation

Intervention

N-acetylcysteine 1200 mg or 2400 mg a day.

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Eligibility criteria

Inclusion criteria

1. High performance liquid chromatography confirmed diagnosis of HbSS, HbSC or HbSâ genotype .
2. Aged 18-65 years

3. Written informed consent

Exclusion criteria

1. Bloodtransfusion in the preceding four months.
2. Pregnancy or the desire to get pregnant in the following 7 months.
3. Concommitant use of hydroxyurea, vitamin K antagonists or other oral anticoagulants, or contraindications for NAC.
4. Impaired renal function of more than 60% (as assessed by the Kockroft-Gauld equation)
5. Known gatsric or duodenal ulcer
6. Concomittant use of anti-hypertensives, sildefanil or nitrates.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2007
Enrollment:	10
Type:	Anticipated

Ethics review

Positive opinion

Date:	03-07-2007
Application type:	First submission

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
NTR-new	NL985
NTR-old	NTR1013
Other	:
ISRCTN	ISRCTN28828586

Study results

Summary results

(1) Duits AJ, Schnog JB, Lard LR, Saleh AW, Rojer RA. Elevated IL-8 levels during sickle cell crisis. Eur J Haematol 1998; 61(5):302-305.
(2) Duits AJ, Rojer RA, van ET et al. Erythropoiesis and serum sVCAM-1 levels in adults with sickle cell disease. Ann Hematol 2003; 82(3):171-174.
(3) Duits AJ, Rodriguez T, Schnog JJ. Serum levels of angiogenic factors indicate a pro-angiogenic state in adults with sickle cell disease. Br J Haematol 2006; 134(1):116-119.
(4) Schnog JB, Teerlink T, van der Dijs FP, Duits AJ, Muskiet FA. Plasma levels of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, are elevated in sickle cell disease. Ann Hematol 2005; 84(5):282-286.
(5) Schnog JB, van der Dijs FP, Brouwer DA, Duits AJ, Muskiet FD, Muskiet FA. Plasma homocysteine levels in sickle cell disease and the need for folate supplementation. J Pediatr Hematol Oncol 2000; 22(2):184-185.
(6) Schnog JB, Keli SO, Pieters RA, Rojer RA, Duits AJ. Duffy phenotype does not influence the clinical severity of sickle cell disease. Clin Immunol 2000; 96(3):264-268.
(7) Schnog JB, Kater AP, Mac Gillavry MR et al. Low adjusted-dose acenocoumarol therapy in sickle cell disease: a pilot study. Am J Hematol 2001; 68(3):179-183.
(8) Schnog JB, Mac Gillavry MR, Rojer RA et al. No effect of acenocoumarol therapy on levels of endothelial activation markers in sickle cell disease. Am J Hematol 2002; 71(1):53-55.
(9) Schnog JB, Rojer RA, Mac Gillavry MR, ten CH, Brandjes DP, Duits AJ. Steady-state

sVCAM-1 serum levels in adults with sickle cell disease. Ann Hematol 2003; 82(2):109-113.
(10) Schnog JB, Mac Gillavry MR, van Zanten AP et al. Protein C and S and inflammation in sickle cell disease. Am J Hematol 2004; 76(1):26-32.
(11) Schnog JB, Duits AJ, Muskiet FA, ten CH, Rojer RA, Brandjes DP. Sickle cell disease; a general overview. Neth J Med 2004; 62(10):364-374.
(12) Schnog JB, Teerlink T, van der Dijs FP, Duits AJ, Muskiet FA. Plasma levels of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, are elevated in sickle cell disease. Ann Hematol 2005; 84(5):282-286.
(13) Schnog JJ, Lard LR, Rojer RA, van der Dijs FP, Muskiet FA, Duits AJ. New concepts in assessing sickle cell disease severity. Am J Hematol 1998; 58(1):61-66.
(14) Schnog JJ, Jager EH, van der Dijs FP et al. Evidence for a metabolic shift of arginine metabolism in sickle cell disease. Ann Hematol 2004; 83(6):371-375.
(15) Schnog JJ, Hovinga JA, Krieg S et al. ADAMTS13 activity in sickle cell disease. Am J Hematol 2006; 81(7):492-498.
(16) van der Dijs FP, Schnog JJ, Brouwer DA et al. Elevated homocysteine levels indicate suboptimal folate status in pediatric sickle cell patients. Am J Hematol 1998; 59(3):192-198.
(17) van der Dijs FP, Fokkema MR, jck-Brouwer DA et al. Optimization of folic acid, vitamin B(12), and vitamin B(6) supplements in pediatric patients with sickle cell disease. Am J Hematol 2002; 69(4):239-246.
(18) Biemond BJ, Perzborn E, Friederich PW, Levi M, Buetehorn U, Buller HR. Prevention and treatment of experimental thrombosis in rabbits with rivaroxaban (BAY 597939)--an oral, direct factor Xa inhibitor. Thromb Haemost 2007; 97(3):471-477.
(19) Biemond BJ, Friederich PW, Koschinsky ML et al. Apolipoprotein(a) attenuates endogenous fibrinolysis in the rabbit jugular vein thrombosis model in vivo. Circulation 1997; 96(5):1612-1615.
(20) Biemond BJ, Levi M, ten CH et al. Plasminogen activator and plasminogen activator inhibitor I release during experimental endotoxaemia in chimpanzees: effect of interventions in the cytokine and coagulation cascades. Clin Sci (Lond) 1995; 88(5):587-594.
(21) Biemond BJ, Levi M, Coronel R, Janse MJ, ten Cate JW, Pannekoek H. Thrombolysis and reocclusion in experimental jugular vein and coronary artery thrombosis. Effects of a plasminogen activator inhibitor type 1-neutralizing monoclonal antibody. Circulation 1995; 91(4):1175-1181.
(22) Biemond BJ, Levi M, ten CH et al. Complete inhibition of endotoxin-induced coagulation activation in chimpanzees with a monoclonal Fab fragment against factor VII/VIIa. Thromb Haemost 1995; 73(2):223-230.
(23) Biemond BJ, Levi M, Nurmohamed MT, Buller HR, ten Cate JW. Additive effect of the combined administration of low molecular weight heparin and recombinant hirudin on thrombus growth in a rabbit jugular vein thrombosis model. Thromb Haemost 1994; 72(3):377-380.
(24) Levi M, Biemond BJ, van Zonneveld AJ, ten Cate JW, Pannekoek H. Inhibition of plasminogen activator inhibitor-1 activity results in promotion of endogenous thrombolysis and inhibition of thrombus extension in models of experimental thrombosis. Circulation 1992; 85(1):305-312.
(25) Levi M, Biemond BJ, Stuck A, Wouter ten CJ. The effect of radiological contrast media in animal models of experimental thrombosis. Semin Hematol 1991; 28(4 Suppl 7):27-30.
(26) Levi M, Biemond BJ, Sturk A, Hoek J, ten Cate JW. Variable effects of radiological contrast media on thrombus growth in a rabbit jugular vein thrombosis model. Thromb Haemost 1991;

66(2):218-221.
(27) van Beers EJ, Peters M, Biemond BJ. [Pathophysiology and treatment of sickle-cell disease]. Ned Tijdschr Geneeskd 2005; 149(21):1144-1149.