Effects of the selective mineralocorticoid receptor antagonist eplerenone on extracellular adenosine formation in humans in vivo

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON38928

Source
ToetsingOnline

Brief title
eplerenone and adenosine

Condition

- Coronary artery disorders

Synonym
blood flow, ischemia reperfusion injury

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W,Netherlands Foundation for Cardiovascular Excellence (NFCVE)

Intervention

Keyword: adenosine, eplerenone, forearm blood flow, ischemia reperfusion

Outcome measures

Primary outcome

-To study whether the MR antagonist eplerenone activates CD73 and hereby increases extracellular formation of adenosine in humans in vivo, by using the forearm vasodilator response to the intrabrachial administration of the ENT-inhibitor dipyridamole, as a surrogate for adenosine receptor stimulation.

Secondary outcome

-To study whether eplerenone increases adenosine formation, by measuring forearm blood flow to incremental periods of arterial occlusion, as an endogenous stimulus for adenosine upregulation.

Study description

Background summary

Despite state-of-the-art reperfusion strategies, mortality and morbidity in patients with an acute myocardial infarction remain significant. This is caused, at least in part, by *lethal reperfusion injury*. Therefore, novel therapeutic options to further limit ischemia-reperfusion (IR) injury are urgently needed to improve outcome in these patients.
It has been suggested that the mineralocorticoid receptor (MR) antagonists spironolactone and eplerenone could potentially serve this goal, because these drugs reduce mortality in patients with heart failure. Indeed, recent studies in murine models of myocardial infarction have shown that MR antagonists can directly limit infarct size. In more detail, in vitro studies and studies in animal models of myocardial infarction have reported that spironolactone, eplerenone and/or canrenoate (the active metabolite of spironolactone) reduce myocardial infarction size, and protect against left ventricular remodeling; by

reducing interstitial fibrosis, cardiomyocyte hypertrophy and/or collagen synthesis, preventing apoptosis, improving cardiac function, and reducing mRNA synthesis of (pro-)collagen. The underlying mechanisms of these cardioprotective effects are not yet fully understood, but it has been suggested that the endogenous purine nucleoside adenosine is crucially involved. In a recent animal study, canrenoate caused a dose-dependent reduction in infarction size. This protective effect of canrenoate was completely abolished in CD73 knock-out and adenosine A2b receptor knock-out mice. In rats, eplerenone significantly reduced infarction size, and this beneficial effect was abolished by co-administration of adenosine receptor antagonists. (2) These findings suggest that extracellular formation of adenosine is crucial for the protective effect of MR antagonists on IR injury.
Adenosine is an endogenous purine nucleoside, which is formed by intra-, and extracellular degradation of adenosine monophosphate by the enzyme ecto-5*-nucleotidase, which is also named CD73. Degradation of adenosine occurs in the intracellular compartment. As a consequence, facilitated diffusion of adenosine over the cellular membrane by the equilibrative nucleoside transporter (ENT) is normally directed inwards. Stimulation of membrane-bound adenosine receptors induces various effects, including vasodilation, inhibition of inflammation, and protection against IR-injury. Indeed, endogenous adenosine acts as a key mediater of the infarct size-limiting effect of several drugs.
Measurement of adenosine is extremely difficult (24), because the half life of adenosine in blood is approximately one second, due to rapid uptake and degradation. (25) Indirectly, the effects of substances which resemble the effects of adenosine, could serve as a surrogate for adenosine formation.
Dipyridamole increases the extracellular adenosine concentration by inhibition of the ENT transporter (26) and induces local vasodilation. (27) Therefore, increase in forearm blood flow (FBF) response to dipyridamole acts reflects adenosine formation.
Dipyridamole increases FBF and this effect is blocked by caffeine. (28) Statins have been shown to promote adenosine receptor stimulation by activation of ecto-5*-nucleotidase activity. (29-31) Metformin facilitates adenosine receptor stimulation, probably by increasing the intracellular formation of adenosine. (32) Arterial occlusion is an endogenous stimulus to increase adenosine formation and hereby enhancing blood flow, resulting in so-called *post-occlusive reactieve hyperemia* (PORH). This effect is also potentiated by dipyridamole and prevented by co-administration of caffeine. (33)

Study objective

In this research proposal, we aim to investigate for the first time in humans in vivo whether eplerenone promotes adenosine receptor stimulation by activating CD73. The results of these studies will provide a possible explanation for the positive effects of MR antagonists on IR-injury. To test our hypotheses, we will use the vasodilator response in the forearm vascular bed to various stimuli as a well-validated surrogate of adenosine receptor

stimulation, as will be explained in more detail in the next section.

Study design

Single center, double blinded, randomized, placebo controlled trial in a cross-over design

Intervention

-eplerenone 50mg bid during 8 days and placebo 50mg bid during 8 days (or vice versa)

Study burden and risks

Nature and extent of the burden:
-participants will visic our clinic 9 times in total
-before inclusion in the study, volunteers will be screened by history taking, physical examination, venous blood drawing (1 time) and electrocardiography
-During the study, participants take eplerenone 50mg bid during 8 days, followed by placebo 50mg bid during 8 days, or vice versa. Venous blood sampling will be performed 6 times during te study, and a 27 gauge-needle will be inserted into the brachial artery 4 times (day 7 and 8 during eplerenone treatment, and day 7 and 8 when on placebo). Participants are not allowed to take any caffeine or alcohol 24 hours before both experiments.

Risks:
-The risk of an hematoma will be very small, because for the insertion of a needle into the brachial artery we use a very small needle (27 gauge).
-we will reduce the risk of hyperkalemia by excluding volunteers with a serum potassium of 4.8 mmol/L or higher. During the first week of treatment we will monitor serum potassium again. At this time, participants will be excluded from the study if they reach a serum potassium of 5.1 mmol/L or higher.
-Although we don't expect an effect on blood pressure during eplerenone treatment in our healthy volunteers, we will exclude male volunteers with a blood pressure of <100/<60 mmHg.
-we don't expect endocrine side effects to occur in our volunteers, since eplerenone is a selective mineralocorticoid receptor antagonist. Therefore, anti-androgenic or progestagene side effects (as seen during spironolactone treatment) are not likely to occur. Furthermore, treatment is only 8 days.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 21
Nijmegen 6525EZ
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 21
Nijmegen 6525EZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy, male, age 18-40 years, written informed consent
(see also chapter 4.2 (Inclusion criteria) of the protocol)

Exclusion criteria

smoking, history of cardiovascular disease, hypertension, renal dysfunction, serum potassium > 4.7 mmol/L
(see also chapter 4.3 (Exclusion criteria) of the protocol)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2013
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Inspra
Generic name:	eplerenone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-03-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-03-2013
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	EUCTR2013-000189-12-NL
CCMO	NL43234.091.13

Study results

Date completed:	24-12-2013
Actual enrolment:	14