Does caffeine reduce dipyridamole-induced protection against ischemia-reperfusion injury?

Published: 11-12-2006
Last updated: 09-05-2024

The purpose of this project is to explore the interaction between caffeine and dipyridamole on ischemia-reperfusion injury in the forearm.

Ethical review	Approved WMO
Status	Pending
Health condition type	Arteriosclerosis, stenosis, vascular insufficiency and necrosis
Study type	Interventional

Summary

ID

NL-OMON30237

Source
ToetsingOnline

Brief title
dipy001

Condition

- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
infarction, ischemic 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,NWO ZonMW

Intervention

Keyword: cafeine, dipyridamole, ischemic preconditioning, ischemic reperfusion injury

Outcome measures

Primary outcome

Percentage difference in radioactivity (counts/pixel) between experimental and control thenar muscle at 60 and 240 minutes after reperfusion.

Secondary outcome

Dipyridamole concentration (after 7 days administration of dipyridamole 200mg twice daily), ENT-activity in erythrocytes before and after 7 day treatment with dipyridamole, and workload during ischemic exercise.

Study description

Background summary

Dipyridamole has several pharmacological properties including phosphodiesterase inhibition, inhibition of the equilibrative nucleoside transporter (ENT1) and scavanging of free radicals. Of these properties, inhibition of the equilibrative nucleoside transporter has been characterized in detail in humans in vivo. Based on this action of dipyridamole, we hypothesized that this drug prevents ischemia-reperfusion injury by augmenting the protective actions of endogenous adenosine. This hypothesis was recently confirmed in our forearm model of ischemia-reperfusion injury with annexin A5 scintigraphy as read-out variable. In this model, dipyridamole appeared to be protective against ischemia-reperfusion injury. Although this study has demonstrated significant ex-vivo inhibition of ENT1 on erythrocytes by dipyridamole, other properties of dipyridamole could still be responsible for this observed benefit.
Caffeine is a rather potent competitive antagonist of adenosine receptors in-vitro and in-vivo. In humans, we have shown that caffeine inhibits adenosine-induced vasodilatation. Furthermore, caffeine inhibits the hemodynamic actions of ENT inhibitors in humans in-vivo. Recently, we also have demonstrated that caffeine prevents the protective action of ischemic preconditioning in our forearm ischemia-reperfusion model as well as in an ex-vivo human atrial model. In this study, caffeine did not affect annexin A5

targetting after ischemic exercise in the absence of ischemic preconditioning.

Study objective

The purpose of this project is to explore the interaction between caffeine and dipyridamole on ischemia-reperfusion injury in the forearm.

Study design

20 Healthy male volunteers will receive a one-week treatment with dipyridamole (slow release; 200 mg twice daily). On day 7, volunteers will visit the research centre after a 24 hour abstinence from caffeine containing beverages. Here caffeine (4 mg/kg) or placebo will be infused intravenously in 10 minutes in a randomized double-blind fashion. 30 Minutes thereafter ischemic isometric muscle contraction of the non dominant forearm will be performed. Upon reperfusion radiolabeled Annexin A5 is injected intravenously. Annexin A5 retention will be recorded by nuclear imaging of both hands 60 and 240 minutes after injection of Annexin A5. The non-exercising hand serves as an internal control for non-specific Annexin A5 binding.

Intervention

10 Volunteers receive coffeine 4mg/kg intravenously just before ischemic exercise. The other 10 volunteers will receive placebo (0,9% NaCl).

Study burden and risks

This study will be executed at the Clinical Research Centre Nijmegen under close medical supervision. All medical personnel at the research centre has been trained in basic life support, including the use of an assisted electric defibrillator (AED), which is available at the research centre.
Treatment with placebo, caffeine or dipyridamole is not expected to harm the volunteers. During the first days of treatment, a headache may occur. Ischemic hand gripping will temporarily result in pain in the forearm. This is completely reversible upon reperfusion.
Administration of radiolabeled annexin A5 results in an effective dose of less than 5 mSv, well within the range of accepted exposure to radioactivity for human research. Participation in this research does not interfere with possible diagnostic or therapeutic procedures with X-rays of radioactivity in the future. For research purposes, volunteers will only be allowed to participate in studies involving radioactivity once per 2 years.
Occurrence of an allergic reaction is theoretically possible upon administration of Annexin A5, however there have been no allergic reaction reported in all volunteers exposed to Annexin A5.
The volunteers will not benefit directly from participating in this study.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

postbus 9101
6500 HB Nijmegen
Nederland
Scientific
Universitair Medisch Centrum Sint Radboud

postbus 9101
6500 HB Nijmegen
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

healthy males, age between 18-50yr

Exclusion criteria

-any concomittant medication
-cardiovascular disease
-hypertension (systole > 140 mmHg, diastole > 90 mmHg)
-hypercholesterolemia (fasting total cholesterol > 5 mmol/l)
-diabetes mellitus (fasting glucose > 7.0 mmol/L or random glucose > 11.0 mmol/L)
-asthma(recurrent episodes of dyspnea and wheezing, or usage of prescribed medications: inhalation corticosteroids or B2-agonists)

-participation in any clinical trial during the last 60 days prior to this study.
-administration of two doses of Annexin A5 (0,1mg; 450MBq) during the last 5 years prior to this study.

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:	Pending
Start date (anticipated):	01-12-2006
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Persantin
Generic name:	Dipyridamol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	11-12-2006
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	EUCTR2006-004878-28-NL
CCMO	NL14457.091.06