Reversal of oral direct factor Xa inhibitors rivaroxaban and apixaban by two different dosages of prothrombin complex concentrate (Cofact®)

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To assess the normalization (reversal) of coagulation assays upon administration of two dosages of Prothrombin Complex Concentratre (PCC, Cofact®) in healthy volunteers treated with either rivaroxaban or apixaban

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular haemorrhagic disorders
Study type	Interventional

Summary

ID

NL-OMON37035

Source
ToetsingOnline

Brief title
Reversal of novel oral anticoagulants by prothrombin complex concentrate

Condition

- Vascular haemorrhagic disorders

Synonym
use of anticoagulation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,Sanquin,Sanquin Bloedbank

Intervention

Keyword: apixaban, oral direct factor Xa inhibitors, prothrombin complex concentrate, rivaroxaban

Outcome measures

Primary outcome

The primary outcome is the reversal (normalisation) of coagulation assays, at

the end of oral f-Xa inhibitor administration and after the infusion of PCC or

placebo.

Secondary outcome

not applicable

Study description

Background summary

Novel oral anticoagulants (NOACs) were originally designed as alternatives for vitamin K antagonists (VKAs) who lack the possibility of being prescribed in a fixed dose regimen. Rivaroxaban and apixaban are examples of NOACs, both direct factor (f) Xa inhibitors that come with a stable pharmacologic profile and therefore do not require regular monitoring for dose adjustments unlike VKAs. Following several phase III trials, NOACs have been approved for several clinical indications. Even though these antithrombotic agents are already on the market, there is no internationally approved method of reversal. As for any anticoagulant, these drugs can cause potential life threatening bleedings and need to be reversed in case of an emergency procedure. In the absence of a specific antidote, the immediate reversal of their anticoagulant effect of a direct fXa inhibitor could be achieved by administration of a prothrombin complex concentrate (PCC), as a recent phase I in vitro study has shown. However, a high dose of PCC was used in this particular study, and a lower dosage may be more practical, less costly and potentially less harmful. Although there is ample experience with PCCs to confirm that they have a low risk of side effects, any prohemostatic agent may increase the risk of thrombosis. Hence, establishing the lowest possible effective dose of PCC is

highly relevant.

Study objective

To assess the normalization (reversal) of coagulation assays upon administration of two dosages of Prothrombin Complex Concentratre (PCC, Cofact®) in healthy volunteers treated with either rivaroxaban or apixaban

Study design

The study will be performed as an investigator initiated, single-centre, double blind, placebo-controlled, randomized, cross-over trial. Subjects will follow three sessions, and they will cross over for the reversal method.
Two groups of 6 healthy male subjects will be enrolled (group 1 and group 2) after a screening phase in which they will be evaluated for eligibility criteria. Subjects in group 1 will take apixaban (h. 8-20 circa) 10 mg twice daily from day -3 to day 0. Subjects in group 2 will take rivaroxaban (h. 8-20 circa) 15 mg twice daily from day -2 to day 0. The final dose of either anticoagulant will be taken on the morning of day 0 without the consumption of food.
After 3 hours from the final dose of the anticoagulant (on day 0) volunteers will receive a single bolus of 25 IU/kg PCC (Cofact®), or a single bolus of 37.5 IU/kg PCC (Cofact®), or placebo (saline). The infusion will be administered intravenously in 30 minutes.
Volunteers will be randomized at the first visit (Day -3 or -2 for apixaban and rivaroxaban respectively) for the reversal method (PCC Cofact® 25 IU/kg; PCC Cofact® 37.5 IU/kg; or saline). Volunteers will be randomized in a fixed ratio of 1:1:1 to placebo (saline), PCC (Cofact®) 25 IU/kg or PCC (Cofact®) 37.5 IU/kg. After a wash out period of 18 days, all subjects will return to the same anticoagulant (apixaban/rivaroxaban), but they will cross-over for the method of reversal and receive a method of reversal that they did not get the previous round (either PCC (Cofact®) 25 IU/ kg or 37.5 IU/kg, or a similar volume of saline). Following another wash-out period of 18 days, all subjects will receive the same anticoagulant (apixaban/rivaroxaban), but will again cross-over for the method of reversal and receive the method of reversal they have not been given in the previous rounds (PCC (Cofact®) 25 IU/ kg or 37.5 IU/kg, or a similar volume of saline). Each session a different reversal method will be given, so that each volunteer will receive all reversal methods in the three different sessions.
The order of treatment will be kept double blind throughout the study. Subjects will be unblinded to the anticoagulant but blinded to placebo (saline) or PCC (Cofact®).
Blood samples will be collected at the following times: T = screening visit, T = day -3 or -2 (before starting apixaban and rivaroxaban, respectively), T = day 0 (before the administration of PCC Cofact®/ saline), and after the administration of PCC Cofact®/ saline at T = 15 min, 30 min, 60 min, 120 min,

240 min, 360 min and at 24 hours (Day 1).

Intervention

Intravenous administration of PCC (Cofact) 25 IU/kg or PCC (Cofact) 37.5 IU/kg or placebo (saline)

Study burden and risks

Subjects will be screened before the randomization and instructed. Subjects treated with apixaban will start with the anticoagulant at day -3; subjects treated with rivaroxaban will start at day -2. They will take the last dosage of anticoagulant without the consumption of food on the morning that they are admitted to the study centre on day 0. Blood samples are collected at the following times: T = screening period, T = day of randomisation, day -2 or -3 (for apixaban and rivaroxaban respectively, before starting the oral anticoagulants), T = day 0: before the administration of PCC (Cofact®) 25 IU/ kg or 37.5 IU/kg, or a similar volume of saline, and after the administration of PCC Cofact®/saline at T = 15 min, 30 min, 60 min, 120 min, 240 min, 360 min and at 24 hours. PCC (Cofact®) and saline are administered 3 hours after the ingestion of the anticoagulant.
After a period of 18 days of wash out, the same procedure will be repeated using the same anticoagulant, but a method of reversal that was not given the previous round (PCC (Cofact®) 25 IU/ kg or 37.5 IU/kg , or a similar volume of saline). After a period of 18 days of wash out, the same procedure will be repeated using the same anticoagulant, but with the method of reversal that has not been given in the previous rounds (PCC (Cofact®) 25 IU/ kg or 37.5 IU/kg, or a similar volume of saline). Each session a different reversal method will be given, so that each volunteer will receive all reversal methods in the three different sessions.
An intravenous catheter will be placed to administer PCC (Cofact®) or saline, and a second intravenous catheter will be inserted for blood withdrawal on the day of PCC Cofact®/saline administration (day 0). Blood samples at other timepoints will be obtained by venapunctures.

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 male subjects as documented by laboratory screen tests (including HIV/HBV/HCV screening), personal medical history and normal physical examination.
* Age *18 years, < 50 years.
* No personal history of thrombotic disease/bleeding disorders.
* No significant family history of thrombotic disease/bleeding disorders, such as recurrent thrombotic/bleeding events or thrombotic/bleeding events in the absence of any risk factors.
* Able to provide written informed consent.

Exclusion criteria

Exclusion criteria are:
* History of allergic reaction to blood products.
* Current participation in any other investigational drug study or within the past 30 days.
* Presence of any condition that, as judged by the investigator, would place the subject at increased risk of harm if he participated in the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-02-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cofact
Generic name:	Prothrombin complex concentrate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Eliquis
Generic name:	apixaban
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xarelto
Generic name:	rivaroxaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	27-11-2012
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-003529-35-NL
CCMO	NL41621.018.12