The ex-vivo potency of Edoxaban in patients with cirrhosis

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Primary Objective: To assess the ex-vivo anticoagulant potency of Edoxaban in patients with Child Pugh A/B cirrhosis, by means of percentual changes in ex-vivo thrombin generation from baseline compared to steady state. These results will be...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON45987

Source
ToetsingOnline

Brief title
POET study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Hepatic and hepatobiliary disorders

Synonym
end stage liverdisease, Fibrosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cirrhosis, DOAC, Edoxaban, Thrombosis

Outcome measures

Primary outcome

This study will measure the percentual difference in thrombin generation capacity of plasma taken at baseline versus plasma taken at steady state in patients with cirrhosis and healthy controls. The main endpoint of the study is the difference between the anticoagulant potency (as expressed by percentual decrease in thrombin generation) of edoxaban in patients compared to controls.

Secondary outcome

This study will also look into the occurence of adverse events and the plasma levels of Edoxaban compared to an anti-Xa assay (calibrated for Edoxaban). Adverse events will be divided into several categories; death, major bleeding, moderate bleeding and mild bleeding events. Major bleeding events are defined as a bleeding at a critical site, a bleeding leading to a loss of 2g/dl of hemoglobin or requiring transfusion of more than two units of blood. Moderate bleeding events do not meet the criteria for major bleeding events but do require medical intervention of transfusion. Mild events do not require intervention or discontinuation of the study drugs.

Other end-points: Prothrombin time, activated partial prothrombin time, D-dimer, factor I and II.

Study description

Background summary

The liver is the site of synthesis for many proteins involved in hemostasis. Consequently, patients with end-stage liver disease (i.e., cirrhosis) acquire multiple and complex alterations in their hemostatic system. Recent insights in consequences of the hemostatic changes in patients with cirrhosis have indicated a balanced, but unstable hemostatic system in these patients with a risk for both bleeding and thrombosis. Prevention and treatment of thrombotic events are a particular challenge due to a frequently prolonged baseline international normalized ratio (INR) and substantially decreased levels of antithrombin, impeding correct dosing and monitoring of respectively vitamin K antagonists (VKA) and heparins. There is very limited clinical experience with the new-generation direct oral anticoagulants (DOAC) in patients with cirrhosis, as these patients were excluded from all clinical trials with these new agents. However, DOACs have potential advantages over other anticoagulants, such as the oral route of administration, the lack of requirement of laboratory monitoring, and the wider therapeutic window, which has resulted in increasing interest from the hepatology community.

Currently four DOACs are registered in Europe for the use of prevention or for the treatment of venous thrombo-embolism and the prevention of cerebrovascular events in patients with non-valvular atrial fibrillation. Edoxaban was found to be non-inferior to warfarin in the prevention of CVE in atrial fibrillation and symptomatic thrombo-embolism. Besides, Edoxaban shows a more favourable risk profile with 2.75% incidence of major bleedings versus 3.43% when compared to Warfarin.

None of the DOACs is officially registered for the cirrhotic population. Nevertheless, a growing number of patients with cirrhosis are treated with these new drugs, despite no clinical information on safety and efficacy. Intagliata et al presented a retrospective cohort in which 20 cirrhotic patients were succesfully treated with factor Xa inhibitors. The number of reported bleeding events was similar between patients treated with DOACs and patients treated with traditional anticoagulants. A number of case reports and a report from the Vascular Liver Disease Group (a European consortium on vascular liver diseases) underline the findings of Intagliata.
Cautious use of some factor Xa inhibitors within mild to moderate cirrhosis is recommended by the manufacturers. The route of clearance of Edoxaban is mainly renal (50%). The remainder of the drug is cleared through hepato/biliary excretion and a minor part (<4%) through CYP450 metabolisation. Therefore, the main concern regards potentially higher plasma concentration of the anticoagulant due to drug accumulation which will increase bleeding risk. In a small group of patients with Child Pugh A and B cirrhosis a single gift of Edoxaban 15 mg was administered. The pharmokinetics and pharmacodynamics of Edoxaban were compared to a cohort of healthy matched controls. The overall exposure of Edoxaban was similar between the patients with Child Pugh B disease

and their matched healthy controls.

In addition to concerns on drug accumulation, in vitro studies performed by our laboratory showed profoundly altered anticoagulant effects of both the traditional anticoagulants and DOACs in patients with cirrhosis. In general, pharmacokinetic studies report plasma levels of anticoagulant drugs, or assays indirectly measuring plasma levels of drug (such as anti-Xa assays) in combination with routine diagnostic tests of coagulation such as the prothrombin time (PT) or activated partial thromboplastin time (APTT). None of these tests, however, truly assesses the extent of the anticoagulant effect. Routine diagnostic tests of coagulation universally fail to test the hemostatic capacity of a blood sample, as these tests are only senisitive for plasma levels of procoagulant proteins. This is a particular concern in patients with liver diseases who have complex alterations in both pro- and anticoagulant pathways. The results of routine diagnostic tests of hemostasis, therefore have long been misinterpreted. We and others have used the thrombin generation test, a research tool developed in the Netherlands, which is now distributed by a large hemostasis diagnostics firm, to better assess the hemostatic status of patients with cirrhosis. The thrombin generation test has many advantages over tests such as the PT and APTT, but the main reason for us to use this test is that it gives an accurate representation of the balance between pro- and anticoagulant factors. A disadvantage of the thrombin generation test is that it is cumbersome and therefore not yet ready for clinical use. In addition, the between laboratory variation in the test is high, although the within laboratory variation is excellent, also in our own experience.
Thrombin generation tests have been used to estimate the efficacy of reversal strategies for DOACs. Specifically, it has been shown that the ex vivo anticoagulant effect of Rivaroxaban and Dabigatran as measured by thrombin generation tests is reversed by prothrombin complex concentrates or recombinant factor VIIa.

We and others have shown that thrombin generation in patients with cirrhosis is equal or even better than that in healthy individuals, which contrasts sharply with the results from PT and APTT tests which are prolonged in patients. Results of the thrombin generation test have been instrumental in changing concepts of management of hemostatic disorders in patients with liver disease, and have led to the realisation that many patients with cirrhosis require anticoagulant therapy despite the fact that the PT/APTT suggest that these patients are *auto-anticoagulated*.

The increasing use of anticoagulant drugs in patients with liver disease has led to yet unsolved clinical questions on the optimal use of these drugs in these patients. Although patients with cirrhosis appear to have intact thrombin generating capacity, their hemostatic system is tremendously altered, which may have consequences for the functionality of pro- and anticoagulant drugs. Indeed, using thrombin generation tests it was demonstrated that low molecular weight heparin is more potent in plasma from patients with cirrhosis compared

to healthy individuals. Subsequently, we performed a systematic in vitro study assessing potential potency changes of all clinically used anticoagulants in patients with cirrhosis. We showed that some anticoagulants, when added to plasma in vitro, had an increased and some had a decreased anticoagulant effect in plasma from patients with cirrhosis as compared to control plasma, Specifically, the Xa inhibiting DOACs were shown to be less potent in patients with cirrhosis whereas IIa directed DOACs showed an increased potency.
Would these potency differences be clinically relevant, dose-adjustments for patients with cirrhosis may be required. However, before embarking on clinical studies testing (dose-adjusted) clinical effects of DOACs in patients with cirrhosis, it is vital to assess whether the potency differences we have observed in vitro, are also present when drugs are actually administered to the patient. Importantly, our previous in vitro studies did not account for altered clearance and metabolisation of the drugs in patients with cirrhosis.

In this study we therefore want to provide the clinical information on the ex-vivo potency of Edoxaban by comparing thrombin generation tests before and after drug administration of cirrhotic patients to matched healthy controls.
The potency of Edoxaban will be estimated by calculating the percentual decrease in thrombin generation following drug administration.

Study objective

Primary Objective: To assess the ex-vivo anticoagulant potency of Edoxaban in patients with Child Pugh A/B cirrhosis, by means of percentual changes in ex-vivo thrombin generation from baseline compared to steady state. These results will be compared with similar measurements in healthy matched controls.

Secondary Objective: The secondary objective of this trial is to determine the safety of the anticoagulant drug Edoxaban in patients with cirrhosis.

Study design

This study has a case controlled interventional design in which patients with cirrhosis will be on a daily regimen of 60 mg of Edoxaban during one week.
Several samples will be taken to generate knowledge on the pharmacodynamics of Edoxaban and to assess the safety and the potency of the drug.
We will include sixteen patients with mild to moderate cirrhosis (Child Pugh A or B) and their results will be compared to sixteen matched healthy controls.
Blood samples will be taken before and 2 hours after the first ingestion at day 3 days and day 7 also 2 hours after ingestion.
Patients with cirrhosis will take the study medication when they are in the hospital as in-patients for a screening program to determine eligibility for liver transplantation.

Intervention

Since HIV-positivity is an exclusion criterium each subject will be tested prior to enrolment.

Overview of planned interventions (this will be performed when the subjects are admitted for their screening programme for liver transplantation):

1. Oral administration of Edoxaban 60 mg once a day for 7 days.
2. Daily Assesment of vital parameters
3. Thorough physical examination prior to the first gift of Edoxaban and at day 3 and day 7.
4. Blood samples (18 ml, with sodium citrate as anticoagulant) will be taken at set time points:
a. 30 minutes before the first gift of Edoxaban
b. 120 minutes after the first gift
c. 120 minutes after the third gift
d. 120 minutes after the seventh gift

It is possible that study patients are planned to be admitted for screening for liver transplantation. In this case the study can take place during their admittance. In other cases patients will enter the study as outpatient participants. Study controls will then partially take place in the UMCG and at the participants home. Overview of the location and duration of the controls for outpatient participants:

* Control 1 at the UMCG; 2.5 hrs
Two blood withdrawals (before and after the first gift of edoxaban)
Physical examination
First gift of edoxaban

* Control 2 at the participants* home on day 3; +/- 20 min
Physical examination
Assessment of vital parameters
One blood withdrawal

* Control 3 at the participants* home on day 7; +/- 20 min
Physical examination
Assessment of vital parameters
One blood withdrawal

When possible we will combine the first control together with an outpatient clinic appointment.

Study burden and risks

Due to the delicate balance of the haemostasis within patients with cirrhosis a thrombotic event occurs more frequently compared to the general population. Currently there is sufficient experience with VKA*s and LMWH as anticoagulant

treatment for thrombosis in cirrhosis. Unfortunately VKA*s need to be monitored and LMWH have an inconvenient route of administration. DOAC can be taken orally once a day without the necessity for routine monitoring of the desired dosage. In the general population DOAC have shown to have a similar and in some cases even a more safe risk profile than VKA*s. The first in vitro studies in cirrhotics did not show a difference in the pharmacodynamics between healthy subjects and subjects with cirrhosis. Next to this the clearance is mainly renal so a higher steady state or drug concentration is not to be expected. Therefore we firmly believe that the possible risk of the treatment outweighs the benefit of investigating the potential of DOAC in patients with cirrhosis. Our study population might benefit themselves from these study results in the future.

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

- Age over 18 yrs
- Child Pugh A or B cirrhosis
- Informed consent

Exclusion criteria

* Malignancies
* Renal failure requiring intervention with drugs or dialysis
* Weight under 60 kg
* Active infection
* Use of anticoagulant drugs in the past 10 days
* Use of cyclosporine, dronedarone, erythromycin, or ketoconazole
* Documentation of inherited bleeding disorders
* History of hepatic disease (in the controls)
* History of thrombotic disease
* Recent viral infection (less than two weeks prior to participation)
* Recent (variceal) bleeding or known present varices grade 2-3/3
* Pregnancy
* HIV-infection

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):	16-12-2016
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lixiana
Generic name:	Edoxaban
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-07-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-11-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2016-000294-21-NL
CCMO	NL56975.042.16