Pharmacokinetics and *dynamics of Dabigatran Etexilate and Rivaroxaban in patients requiring PArenteral Nutrition (the PDER PAN study)

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The aim of this phase I study is to assess the extent of intestinal absorption of rivaroxaban and dabigatran etexilate in adult patients with short bowel syndrome and treated with long-term TPN.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON38688

Source
ToetsingOnline

Brief title
AMC_PDER_PAN

Condition

- Embolism and thrombosis

Synonym
anticoagulant, blood thinner

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

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

Intervention

Keyword: dabigatran etexilate, parenteral nutrition, phase I, rivaroxaban

Outcome measures

Primary outcome

The primary outcome is the assessment of PK and PD parameters of the two drugs and the comparison to published values.

Secondary outcome

The secondary outcome is the comparison between rivaroxaban PK parameters and dabigatran PK parameters (AUC, Cmax and Tmax).

PK Parameters

- rivaroxaban plasma concentration (liquid chromatography-mass spectrometry; LC-MS/MS),

- dabigatran plasma concentration (liquid chromatography-mass spectrometry; LC-MS/MS).

Pharmacokinetic parameters will be calculated by non-compartmental analysis. The following parameters will be obtained: Tmax (time of maximal concentration), Cmax (maximal concentration), AUC (area under the plasma versus time curve (dabigatran: 0-12 h, rivaroxaban: 0-24h), CL/F (oral clearance), V/F (volume of distribution) and T1/2 (elimination half life). AUC, Cmax and Tmax will compared to published values.

PD parameters

- aPTT (dabigatran),

- Neoplastin Plus PT (Diagnostica Stago, Asnières, France) (rivaroxaban),

- calibrated quantitative anti-factor Xa assay (STA Rotachrom*method,

Diagnostica Stago, Asnières-sur-Seine, France) (rivaroxaban),

- Hemoclot thrombin inhibitor assay (HYPHEN BioMed, Neuville-sur-Oise, France)

(dabigatran).

Study description

Background summary

Chronic intestinal failure (IF) is caused by either surgically induced anatomical short bowel, severe motility, or absorption disorders. These patients require partial or total parenteral nutrition (PN and TPN, respectively) and are thereby critically dependent on maintaining venous access with a central venous catheter (CVC). Recurrent CVC-related thrombosis is a serious complication and will ultimately lead to loss of central venous access with intestinal transplantation being the only treatment option left.
Therefore, patients at risk for recurrent thrombosis and requiring (T)PN are treated with long-term anticoagulants to prevent CVC-thrombosis, although no prospective studies have assessed the efficacy and the safety of any long-term anticoagulant treatment in these patients.
In patients with a normal intestinal absorption, INR-adjusted vitamin K antagonists (VKAs) are the most used drugs for long-term anticoagulant treatment. Most patients with intestinal failure requiring (T)PN cannot be treated with these orally absorbed anticoagulants. This is due to unstable INR levels mainly caused by variable drug absorption. In addition, most patients do not use (T)PN daily, resulting in fluctuating vitamin K levels. Therefore, subcutaneous low molecular weight heparins (LMWHs) or intravenous warfarin are usually used for long-term anticoagulation in these patients. LMWH is administered by daily subcutaneous injections, which is burdensome for patients and can reduce compliance. Furthermore, LMWHs can lead to adverse reactions, including allergic skin reactions, heparin-induced thrombocytopenia, and osteoporosis.
A new generation of oral anticoagulants (NOACs), including dabigatran etexilate and rivaroxaban, has recently been approved for prevention and the treatment of venous thromboembolism (VTE) and ischemic stroke prevention in patients with atrial fibrillation (AF). In contrast with VKAs, these drugs do not interact with vitamin K metabolism, have a more predictable pharmacokinetic profile,

have less interaction with other drugs, and are prescribed at a fixed dose without routine laboratory monitoring. Importantly, these drugs are absorbed proximally in the gastrointestinal tract (stomach, duodenum, and proximal small bowel). Therefore, NOACs may be an attractive oral alternative to both LMWH injections and VKAs in these patients.

Study objective

The aim of this phase I study is to assess the extent of intestinal absorption of rivaroxaban and dabigatran etexilate in adult patients with short bowel syndrome and treated with long-term TPN.

Study design

The study will be performed as an investigator initiated, single center, randomized, phase I, cross-over study (Figure 1).
Patients will be screened before the randomization and instructed after collecting the informed consent. The treating physician will screen patients for eligibility.
On Day 0 patients will visit the Metabolic Research Unit and randomized in two groups: subjects in Group 1 (n = 3) will take rivaroxaban 20 mg once daily (h 8.00) from Day 0 to Day 4 (five total doses); patients in Group 2 (n = 3) will take dabigatran etexilate 150 mg twice daily (h 8.00-20.00) from Day 0 to Day 4 (nine total doses). The dose of either anticoagulant will be taken without the consumption of food. After a period of at least 4 days of wash-out, patients in both groups will switch to the other NOAC (dabigatran etexilate/rivaroxaban or rivaroxaban/dabigatran etexilate) and the procedure will be repeated. The patients will be randomized in two groups only for the order of NOACs.
Blood samples will be collected at the research unit at the following times: 1) after rivaroxaban administration: - Day 0: T = 0 (= blank), T = 3 hours following the first dose; - Day 4 at steady state: T = 0 (= trough), T = 1, 2, 3, 4, 5, 6, 8, 10, 24 hour(s) following the fifth dose. 2) after dabigatran etexilate administration: - Day 0: T = 0 (= blank), T = 3 hours following the first dose;
- Day 4 at steady state: T = 0 (= trough), T = 1, 2, 3, 4, 5, 6, 8, 12 hour(s) following the ninth dose. At each timepoint 12 mL will be collected: one EDTA blood sample will be collected for determination of rivaroxaban and dabigatran concentrations, and two citrated blood samples will be collected for PD parameters. A total of 276 mL of blood will be collected during the whole study period. Plasma will be separated and stored at -20°C until analysis.
In exceptional situations, according to patient*s preferences and/or in case of major personal limitations, blood samples will be collected at patient*s home (Day 0 sample and T 24 sample only).
NOACs will be administered for 5 days to reach an appropriate steady state level. On the basis of the calculated PK parameters in healthy volunteers, rivaroxaban needs about 35-45 hours and dabigatran needs about 60-70 hours to

reach the steady state. In consideration of a theoretical reduction of the absorption in these patients due to the intestinal resection, and in consideration of a theoretical reduced bioavailability of the drugs, a 5-days NOACs administration is reasonable.
The duration of the study for enrolled subjects can vary from 14 to 30 days according to the length of the wash-out period decided by the patient.

Intervention

Rivaroxaban and dabigatran etexilate will be used in the commercially available formulation and will be obtained through the pharmacy of the Academic Medical Center. Batchnumbers of medication will be recorded. Adherence to study medication will be evaluated at the end of treatment checking the empty box. For the treatment of acute VTE rivaroxaban and dabigatran etexilate have been administrated in clinical trials at the doses used in our protocol (20 mg once-daily and 150 mg twice-daily, respectively).

Study burden and risks

The burden for participants consists of 1) daily drug intake (5+5 consecutive days), 2) one baseline visit before the randomization, and one day visit at the hospital or at the patient*s home with placement of one peripheral venous catheter for the blood samples (twice). An estimated total amount of 160 mL of blood will be drawn per subject during the whole study.
The risks for all subjects participating in this study are the risks of a normal venapuncture and the risk of bleeding due to the use of an anticoagulant. A peripheral venous catheter for the sampling of blood will be temporarily placed. CVC and/or catheter used for PN will not be used for sampling of blood.
In the phase III trials in patients with atrial fibrillation, the risk of major bleeding in patients treated with dabigatran etexilate and rivaroxaban was 2-4% per year. In the phase-III Einstein PE clinical trial rivaroxaban at the same dose of the present study showed an incidence of major bleeding events of 1.1% per patient and estimated in 0.005% per day per patient (mean study treatment duration was 216 days). In the phase-III RE-COVER VTE clinical trial dabigatran etexilate at the same dose of the present study showed an incidence of major bleeding events of 1.6% per patient and estimated in 0.009% per day per patient (mean study treatment duration was 163 days).
The risk of bleeding of 5 days of treatment (twice) is therefore very small. If the absorption in patients requiring TPN would be lower than in non-TPN patients, these bleeding risks will likely be even lower.

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

Inclusion criteria are:
- clinically stable adult male and female patients (age between 18 and 75 years),
- body weight between 50 and 100 kg,
- chronic (>3 months) use of home TPN due to short bowel syndrome after surgical resection and small bowel shorter than 160 cm after ligamentum of Treitz, irrespective of the presence of colon,

Exclusion criteria

Exclusion criteria are:
- moderate/severe renal impairment (CKD EPI Creatinine Clearance < 50 mL/min according to http://www.nephron.com/MDRD_GFR.cgi), or moderate/severe hepatic impairment (class B (7-9 points) or class C (10-15 points) at the Child-Pugh score),
- major bleeding events in the previous 6 months (according with the International Society on

Thrombosis and Haemostasis definition of major bleeding in non-surgical patients),
- cytochrome P450 3A4 and/or P-gp-dependent co-medications in the last 14 days (verapamil, azoles, amiodarone, dronedarone, azithromycin, erythromycin, clarythromycin, quinidine, ritonavir, cyclosporine, propafenone, isoniazid, rifampin, rifapentine, primidone, St. John*s wort, carbamazepine, oxcarbazepine, phenobarbital, pentobarbital, nevirapine, nafcillin, fosphenonytoin),
- ongoing anticoagulant treatment for an acute thrombotic event (prior 6 months) or for a condition estimated to be at high risk of recurrence (i.e., presence of mechanical heart valve),
- use of phenprocoumon,
- chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), or chronic treatment with aspirin (>100 mg/day), or dual antiplatelet therapy,
- current participation in any other investigational drug study or within the past 30 days,
- pregnancy,
- partial or total gastrectomy, and/or resection of the duodenum for any cause,
- 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 (i.e., recent CVC-related infection, sepsis)
- presence of significant haemostatic abnormalities (i.e., severe thrombocytopenia, severe prolongation of haemostatic tests PT and aPTT) in patients that are not being treated with any anticoagulant.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-10-2013
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pradaxa
Generic name:	dabigatran etexilate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xarelto
Generic name:	rivaroxaban
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2013
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	EUCTR2013-000203-16-NL
CCMO	NL42865.018.13