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 requiring long-term TPN.

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON26342

Bron
Nationaal Trial Register

Verkorte titel
the PDER PAN study

Aandoening

parenteral nutrition, thrombosis, pharmacokinetics, pharmacodynamics, anticoagulant

Ondersteuning

Primaire sponsor: Academic Medical Center, Amsterdam, The Netherlands
Overige ondersteuning: Academic Medical Center, Amsterdam, The Netherlands

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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

Toelichting onderzoek

Achtergrond van het onderzoek

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 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 often treated with long-term anticoagulants to prevent CVC-thrombosis, such as INR-adjusted vitamin K antagonists (VKAs) or low-molecular-weght heparins (LMWHs).
A new generation of oral anticoagulants (NOACs), including dabigatran etexilate and rivaroxaban, has recently been approved for several indications. 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.
The aim of the PDER PAN phase I study is to assess the extent of intestinal absorption of rivaroxaban 20 mg once-daily and dabigatran etexilate 150 mg twice-daily at steady state in adult patients with short bowel syndrome requiring long-term TPN.
The primary outcome is the assessment of pharmacokinetics and -dynamics parameters of the two drugs, and the comparison to published values from studies in healthy volunteer.

Doel van het onderzoek

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 requiring long-term TPN.

Onderzoeksopzet

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.

Onderzoeksproduct en/of interventie

In a cross-over design, patients will be treated with either rivaroxaban 20 mg once daily for five days or dabigatran etexilate 150 mg twice daily for five days. Between the two treatment periods, a wash out period of at least 4 days will be applied. After each 5-day period of NOAC use, patients will be admitted for a full pharmacokinetic and –dynamic profile will be obtained with 10 blood samples.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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, defined as symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or red cells),

- 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, due to the difficulties of a proper bridging (drug half-life = 7 days),

- 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 not currently on anticoagulant.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Enkelblind
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-10-2013
Aantal proefpersonen:	6
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	01-10-2013

Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3978
NTR-old	NTR4192
Ander register	42865 : ABR
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A