Implementation of pharmacokinetic-guided dosing of DDAVP and VWF-containing concentrates in von Willebrand disease

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To investigate whether on demand dosing using population-based PK-models in VWD patients is reliable and feasible.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Blood and lymphatic system disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54546

Source
ToetsingOnline

Brief title
OPTI-CLOT: To WiN

Condition

- Blood and lymphatic system disorders congenital

Synonym
bleeding disorder, von Willebrand disease

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Clotting factor concentrate, DDAVP, Pharmacokinetics, Von Willebrand disease

Outcome measures

Primary outcome

A. In case of DDAVP-testing: predictive performance of the DDAVP population PK model: reliability of predicted FVIII and VWF:Act levels (U/ml), defined as difference between predicted and actual FVIII and VWF:Act levels (U/ml).

B. In case of elective medical interventions and treatment with DDAVP or VWF-containing concentrate: predictive performance of the Bayesian adaptive approach using the population PK model for either DDAVP or VWF-containing concentrate: reliability of predicted FVIII and VWF:Act levels (U/ml), defined as difference between predicted and actual FVIII and VWF:Act levels (U/ml) achieved after dosing according to target levels stated by consensus and treating physician.

C. In case of treatment of a bleeding episode with DDAVP or VWF-containing concentrate: predictive performance of the respective population PK models: reliability of predicted FVIII and VWF:Act levels (U/ml), defined as difference between predicted and actual FVIII and VWF:Act levels (U/ml) achieved after dosing.

D. In case of prophylaxis with VWF-containing concentrate: reliability of predicted FVIII and VWF:Act levels, defined as difference between predicted and actual FVIII and VWF:Act levels achieved after dosing (predictive performance).

Secondary outcome

1. (Only in B & C): number and timing of DDAVP administrations and/or timing

and dosing (U/kg) of VWF-containing concentrate infusions.

2. (Only in B & C): hemostasis as quantified by hemoglobin values (mmol/l), amount of blood loss (ml), incidence of thrombosis, and need for blood transfusion and/or (re)-operation.

3. (Only in B & C): duration of hospitalization (days), clinical visit (days).

4. (Only in B & C): feasibility of intervention with regard to patient and physician satisfaction and economic impact.

5. (Only in case of DDAVP-testing or DDAVP-treatment): DDAVP plasma concentrations (pg/ml).

6. (only in D): Association of (real life or simulated) FVIII and VWF:act (trough and peak levels) with bleeding episodes.

Study description

Background summary

Von Willebrand disease (VWD) is an inherited bleeding disorder, caused by a deficiency or abnormal function of von Willebrand factor (VWF). In the circulation, VWF is bound to Factor VIII (FVIII), protecting it from proteolysis. Severe deficiency of VWF, or a specific defect in interaction with FVIII, causes a secondary moderate deficiency of FVIII. It is well known that there is large intra- and interindividual variability in plasma VWF levels, due to different factors.

Goal of on demand treatment in VWD patients is to stop or prevent (re)bleeding by increasing or normalizing plasma VWF and FVIII levels. This can be done by stimulation of the release of endogenous VWF by administration of DDAVP, or by infusing VWF-containing concentrates. Choice of treatment is dependent on type of disease, contraindications for DDAVP, and severity of the bleeding or procedure.

Interindividual response to DDAVP differs greatly, but in general, response in the individual patient has been proven to be reproducible and consistent over time. Due to the great interpatient variability in response, a DDAVP test is

required to establish DDAVP response in each individual patient. Patients who do not adequately respond to DDAVP or have contraindications for its* use are eligible for treatment with VWF-containing concentrates, that mostly also contain FVIII. Currently, dosing of medication is based on body weight. During treatment, daily measurements of plasma FVIII and VWF levels are necessary to assess the risk of bleeding due to low levels, or risk of thrombosis due to high levels. From previous research, we know that most VWD patients reach high to very high FVIII levels during treatment, and could possibly be dosed lower.

Population pharmacokinetic (popPK) models have recently been constructed for treatment of VWD with DDAVP and VWF-containing concentrates, enabling individualized dosing in these patients.

Study objective

To investigate whether on demand dosing using population-based PK-models in VWD patients is reliable and feasible.

Study design

Multicenter, non-randomized, open label, cohort study in VWD patients undergoing DDAVP-testing and VWD patients requiring treatment with DDAVP and/or VWF-containing concentrate during a medical intervention or during a bleeding episode and patients receiving or requiring prophylaxis with VWF containing concentrate due to frequent bleeding episodes.Frequency and timing, and dosing (only in case of VWF-containing concentrate treatment) of administration will be based on a pre-operatively constructed individual PK model.

Intervention

All patients will be treated with the same commercially available DDAVP or VWF-containing concentrate as they would be treated with during standard treatment. Patients will not switch products for study purposes.

DDAVP-testing:
Newly diagnosed VWD patients undergo DDAVP-testing to investigate the individual response to DDAVP. In patients needing to undergo a DDAVP-test, a prediction of the FVIII and VWF:Act levels reached after infusion of DDAVP will be made on basis of patient characteristics, using the DDAVP population PK model.

On demand treatment:
Most patients are treated on demand. During elective dental or surgical procedures and during bleeding episodes, we will aim for FVIII and VWF:Act target plasma levels as defined in the National Hemophilia Consensus. However, the treating physician will be able to set specific FVIII and VWF activity

(VWF:Act) target levels if clinically indicated due to the patients* bleeding phenotype or severity of the procedure or bleeding. These patient specific target levels will be carefully recorded prior to treatment and communicated to the clinical pharmacologist performing the PK modeling. The clinical pharmacologist will provide individualized dosing advices for targeting FVIII and VWF levels as communicated by the treating physician, based on the PK-model and daily measurements of FVIII and VWF:Act.

Prophylactic treatment
A few VWD patients receive prophylactic treatment with VWF-containing concentrate. The aim of prophylactic treatment is to prevent spontaneous bleeding in VWD patients who experience frequent and/or severe (spontaneous) bleeding. We will aim for FVIII and VWF:Act target plasma levels as defined in the National Hemophilia Consensus. However, the treating physician will be able to set specific FVIII and VWF activity (VWF:Act) target levels if clinically indicated due to the patients* bleeding phenotype.These patient specific target levels will be carefully recorded prior to treatment and communicated to the clinical pharmacologist performing the PK modeling. The clinical pharmacologist will provide individualized dosing advices for targeting FVIII and VWF levels as communicated by the treating physician, based on the PK-model and measurements of FVIII and VWF:Act.

Individual PK profiling:
For every patient an individualized dosing advice will be provided based on body weight, type of procedure/bleeding, target FVIII and VWF:Act levels perioperatively/during the bleeding episode, baseline FVIII and VWF:Act level and individual pharmacokinetic profile.

Individual DDAVP PK profile (DDAVP-test):
DDAVP-tests, which can be seen as an individual DDAVP PK profile, will be performed according to normal protocol.

Individual VWF-containing concentrate PK profile:
Patients undergoing a medical intervention with replacement therapy with VWF-containing concentrate, will be asked to undergo a PK profile with approximately 25 U/Kg Haemate P®. Blood sampling for FVIII and VWF will be performed before (t=0) and at 4 time points within 48 hours after bolus infusion; namely t = peak (10 minutes after stop of infusion), t=2-6 hours, t = approximately 24 hours and t = approximately 48 hours after stop of infusion. Additional parameters will be tested according to protocol.

Population pharmacokinetic models:
Population PK models for DDAVP and VWF-containing concentrates have been constructed using the software program NONMEM®. These models are able to predict average PK parameters for FVIII in a population of VWD patients as well as the inter- and intra-patient variability of these PK parameters.

In the models the relationship between different patient- and treatment factors, such as age, weight, baseline FVIII and VWF, blood type and VWF levels and pharmacokinetic parameters is described. This allows the a priori prediction of the PK profile of FVIII after DDAVP and VWF-containing concentrate administration.
Population PK- models for VWF:Act are currently being developed and will be applicable before start of the study.

Study burden and risks

There are no additional risks compared to the standard treatment due to intensive monitoring of FVIII/VWF plasma levels. As it has been shown that patients are often dosed too high, or to low, based on their body weight, it is important to explore other ways of dosing (i.e. PK-guided dosing). This may enable better targeting of FVIII/VWF plasma levels, with a possible reduction of complications and reduction of costs by reducing the amount of factor concentrate used.
The risks of performing the PK-profile are small (hematoma or inconvenience due to failure of venipuncture). In young children or patients with impaired venous access, we will try to apply a intravenous catheter, to draw blood at different time points without having to do repeated punctures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- No minimum or maximum age at inclusion date;
- Hemorrhagic symptoms or a family history of von Willebrand disease with historically lowest levels of VWF:Ag <0.60 IU/ml and/or VWF:Act <0.60 IU/ml and/or VWF:CB <0.60 and/or FVIII <0.40 IU/ml;
- Need for DDAVP-testing (arm A); and/or
- Need for a medical intervention requiring DDAVP and/or VWF replacement therapy (arm B) (arm B); or
- (Future) Bleeding requiring DDAVP and/or VWF replacement therapy (arm C); or
- Receiving or requiring prophylaxis with VWF-containing concentrate due severe and/or recurrent bleeding episode (arm D).
- Written patient (and in case of a patient <16 years of age, parental) informed consent.

Exclusion criteria

- Any other known hemostatic abnormalities;
- Acquired VWD;
- Presence of VWF antibodies (>0.2 BU)
- Withdrawal of (parental) informed consent.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-04-2019
Enrollment:	250
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Haemate P / Humate P
Generic name:	Human coagulation factor VIII/human von Willebrand factor complex concentrate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Minrin
Generic name:	Desmopressin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Octostim
Generic name:	Desmopressin i.n.
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Octostim
Generic name:	Desmopressin intravenous or subcutaneous
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Wilate
Generic name:	Human coagulation factor VIII/human von Willebrand factor complex concentrate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-02-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	13-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2025
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 20178
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2018-001631-46-NL
CCMO	NL65876.078.18