Implementation of pharmacokinetic (PK)-guided dosing of DDAVP and VWF-containing concentrates in von Willebrand disease and low VWF

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Using newly developed population pharmacokinetic models for DDAVP and VWF-containing concentrate in von Willebrand disease (VWD), clotting factor levels (FVIII and VWF:Act) after dosing of DDAVP or VWF-containing concentrate can be reliably...

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

Samenvatting

ID

NL-OMON20178

Bron
Nationaal Trial Register

Verkorte titel
OPTI-CLOT: To-WiN

Aandoening

Von Willebrand disease, pharmacokinetics, treatment, bleeding, surgery

Ondersteuning

Primaire sponsor: Erasmus University Medical Center - Sophia Children's Hospital, University Medical Center Rotterdam
Overige ondersteuning: Innovatiefonds Zorgverzekeraars

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

A. In case of DDAVP-testing: predictive performance of the DDAVP population PK model: reliability of predicted VWF:Act and FVIII levels (IU/ml), defined as difference (%) between predicted and actual VWF:Act and FVIII levels (IU/ml).
B. In case of elective procedures 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 VWF:Act and FVIII levels (IU/ml) , defined as difference (%) between predicted and actual VWF:Act and FVIII levels (IU/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 VWF:Act and FVIII levels (IU/ml), defined as difference (%) between predicted and actual VWF:Act and FVIII levels (IU/ml) achieved after dosing.
D. In patients receiving prophylaxis with a VWF-containing concentrate: predictive performance of the respective population PK models: reliability of predicted VWF:Act and FVIII levels (IU/ml), defined as difference (%) between predicted and actual VWF:Act and FVIII levels (IU/ml) achieved after dosing.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale:

Von Willebrand disease (VWD) is a bleeding disorder caused by a deficiency or defect of von Willebrand factor (VWF). In case of bleeding or surgery, patients are treated with desmopressin (DDAVP) or VWF-containing concentrates. Aim of treatment is to achieve hemostasis by reaching physiologically normal plasma coagulation factor levels. There are large inter- and intraindividual differences in effect of treatment. This can be explained by differences in pharmacokinetics (PK) of medication in each individual. Population PK models have been constructed describing the response of FVIII and VWF after administration of both DDAVP and VWF-containing concentrates. PK-guided dosing may greatly improve the efficacy of therapy. It is however essential to also evaluate the feasibility of this approach prospectively, in order to prove its effectiveness and safety.

Study objective:

To prospectively investigate the reliability and feasibility of PK-guided dosing of DDAVP and/or VWF-containing concentrate in VWD patients.

Study Design:

Multicenter, non-randomized, open label, cohort study.

Study Population:

- Patients of all ages, with all types of VWD and low VWF;

- Scheduled to undergo a DDAVP-test, and/or;

- Scheduled to undergo an elective medical procedure (e.g. dental extraction, surgical procedure), requiring treatment with DDAVP and/or VWF-containing concentrate, or;

- With bleeding requiring treatment with DDAVP and/or VWF-containing concentrate, or;

- Receiving or requiring prophylactic treatment with a VWF-containing concentrate

Intervention:

The feasibility/predictive performance of PK-guided dosing will be tested in 4 situations:

A. Patients receiving a DDAVP test dose. The PK profile be will be predicted a priori on basis of the constructed population PK-model.

B. In patients undergoing a dental or surgical procedure, results obtained from a prior individual DDAVP-test will be used to establish frequency of dosing before the dental or surgical procedure. Patients who are not eligible for DDAVP administration, due to contraindications for its use, or due to type of VWD, will undergo individual PK profiling after a standard bolus infusion of VWF-containing concentrate. During the elective dental or surgical procedure, patients will be dosed with DDAVP and/or VWF-containing concentrate on basis of their individual PK parameters as derived by Bayesian analysis. The reliability of predicted results after infusion of DDAVP and VWF-containing concentrate on FVIII and VWF plasma levels will be tested. During the perioperative period Bayesian analysis will be applied allowing iterative dosing (amount, frequency) adjustment of DDAVP and VWF-containing concentrates.

C. In patients with a bleeding episode requiring treatment with DDAVP and/or VWF-containing concentrate with monitoring of FVIII and VWF levels, these levels and dosing of DDAVP and/or VWF-containing concentrate after the initial DDAVP or VWF-containing concentrate dose will be predicted on basis of the population PK models.

D. In patients receiving prophylaxis with a VWF-containing concentrate due to frequent bleeding episodes, patients will first undergo PK-profiling in order to determine the optimal dosage of VWF-containing concentrate on basis of VWF:Act or FVIII target trough and peak values as set by the treating physician and patients' individual PK parameters as derived by

Bayesian analysis. Patients will initially receive PK-guided treatment for 12 weeks. During this period, plasma concentrations will be tested and compared to predicted VWF:Act and FVIII to validate the advised dosing regimen. Bleedings episodes will be obtained from medical records. A subsequent follow-up period of 24 weeks is necessary to collect additional data and to analyze the association between plasma VWF:Act and FVIII and bleeding events.

Primary endpoints:

A. Predictive performance of the DDAVP population PK model: reliability of predicted FVIII levels, defined as difference between predicted and actual FVIII levels.

B. Predictive performance of the Bayesian adaptive approach using the population PK model for either DDAVP or VWF-containing concentrate: reliability of predicted FVIII levels, defined as difference between predicted and actual FVIII levels achieved after dosing according to target levels stated by consensus and treating physician.

C. Predictive performance of the respective population PK models: reliability of predicted FVIII levels, defined as difference between predicted and actual FVIII levels achieved after dosing.

D. Predictive performance of the VWF-containing concentrate population PK models, i.e. reliability of the predicted VWF:Act and FVIII levels, defined as the difference between predicted and actual VWF:Act and FVIII levels achieved after dosing.

Doel van het onderzoek

Using newly developed population pharmacokinetic models for DDAVP and VWF-containing concentrate in von Willebrand disease (VWD), clotting factor levels (FVIII and VWF:Act) after dosing of DDAVP or VWF-containing concentrate can be reliably predicted in case of DDAVP-testing, surgery, bleeding or prophylaxis.

Onderzoeksopzet

Primary outcomes:

A. At time points (at least at time points t = 0 h, 1 h and 3 or 4 h after administration of DDAVP, possibly also at t = 6 h and 24 h).

B+C. From first dose up to 14 days after surgery or bleeding.

D. At 3 time points during the first 12 weeks of PK-guided treatment, at 1 time point during follow-up PK guided treatment (24 weeks)

Secondary outcomes:

1-4. From 1 day before up to 14 days after start of surgery or bleeding, or until end of follow-

up PK-guided treatment.

5. From first dose up to 14 days after surgery or bleeding.

Onderzoeksproduct en/of interventie

A. In patients needing to undergo a DDAVP-test, no intervention will be implemented.

B. In patients requiring treatment with DDAVP and/or VWF-containing concentrate during an elective dental or surgical procedure, frequency and timing, and dosing (only in case of VWF-containing concentrate treatment) of administration will be based on an individual pre-operative PK profile.

C. In patients requiring treatment with DDAVP and/or VWF-containing concentrate during a bleeding episode, frequency and timing, and dosing (only in case of VWF-containing concentrate treatment) of administration will be based on an individual pre-operative PK profile (previous DDAVP-test in case of DDAVP treatment) or on patient characteristics (in case of VWF-containing concentrate treatment).

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- No minimum or maximum age at inclusion date;

- Hemorrhagic symptoms or a family history of von Willebrand disease or low VWF with historically lowest levels of VWF:Ag and/or VWF:Act and/or VWF:Cb <0.60 IU/ml and/or FVIII <0.40 IU/ml (only in type 2N);

- Need for DDAVP-testing; and/or

- Need for a medical procedure requiring DDAVP and/or VWF replacement therapy during the procedure; or

- Bleeding requiring DDAVP and/or VWF replacement therapy; or

- Frequent bleeding requiring prophylaxis with VWF-containing concentrate.

- Written informed consent in patients 12 years and older, and written parental consent in patients <16 years

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Any other known hemostatic abnormalities;

- Acquired VWD;

- Presence of VWF antibodies (>0.2 BU)

- Withdrawal of (parental) informed consent.

Onderzoeksopzet

Opzet

Type: Interventie onderzoek

Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-10-2018
Aantal proefpersonen:	123
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	10-07-2018
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 54546
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7212
NTR-old	NTR7411
EudraCT	2018-001631-46
CCMO	NL65876.078.18
OMON	NL-OMON54546

Resultaten