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...

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20178

Source
NTR

Brief title
OPTI-CLOT: To-WiN

Health condition

Von Willebrand disease, pharmacokinetics, treatment, bleeding, surgery

Sponsors and support

Primary sponsor: Erasmus University Medical Center - Sophia Children's Hospital, University Medical Center Rotterdam
Source(s) of monetary or material Support: Innovatiefonds Zorgverzekeraars

Intervention

Outcome measures

Primary outcome

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.

Secondary outcome

Only applicable in B, C and D:
1. Number and timing of DDAVP infusions and/or timing and dosing (IU/kg) of VWF-containing concentrate infusions.
2. Hemostasis as quantified by hemoglobin values pre- and postoperatively, amount of blood loss (ml), incidence of bleeding and thrombosis, and need for blood transfusion and/or (re)-operation.
3. Duration of hospitalization (days), number of outpatient clinic visits.
4. Feasibility of intervention with regard to patient and physician satisfaction and economic impact.

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

Study description

Background summary

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.

Study objective

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.

Study design

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.

Intervention

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).

Contacts

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Eligibility criteria

Inclusion criteria

- 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

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
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-10-2018
Enrollment:	123
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	10-07-2018
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 54546
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

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

Study results