Clinical validation of a dried blood spot (DBS) method for the analysis of immunosuppressive and antifungal drugs in pediatric patients (part of the PROTECT study).

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PrimairyTo clinically validate a finger prick DBS method compared to conventional venous sampling for the analysis of 5 immunosuppressive and 4 azole antifungal drugs in the pediatric population. Secondairy• Feasibility of the novel finger prick DBS...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON44369

Source
ToetsingOnline

Brief title
PROTECT

Condition

- Other condition
- Fungal infectious disorders

Synonym
analysis of drug used in renal transplantation / analysis of drug used in invasive fungal infections

Health condition

immuunsuppressie na niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Apotheek
Source(s) of monetary or material Support: Ministerie van OC&W,SPARK Holland BV

Intervention

Keyword: DBS, Feasibility, TDM (Therapeutic Drug Monitoring), Validation

Outcome measures

Primary outcome

The primary objective of this study is the clinical validation of a DBS method for voriconazole, fluconazole, itraconazole, posaconazole, mofetil mycophenolic acid, cyclosporine, tacrolimus, sirolimus and everolimus in the pediatric population. The related endpoint will is the evaluation ofbe the association between the concentration obtained by venous sampling and the concentration obtained by means of DBS sampling. The predictive performance of the DBS method as a measure for the venous concentration will be evaluated.

Secondary outcome

- To assess the feasibility of finger prick DBS in the pediatric population.
The related endpoint is the response to a questionnaire. Results will be used to prepare implementation of the novel method for home-based monitoring as well as to prepare a HTA analysis.
- To design an inventory of cost types related to DBS sampling and conventional sampling. The cost types will function as a basis for future HTA analysis of this novel sampling method compared to conventional venous sampling.

- To use the date already collected for the primary endpoint to construct a population pharmacokinetic model to optimize dosing and design new guidelines of the nine compounds included in this study (voriconazole, fluconazole, itraconazole, posaconazole, mofetil mycophenolic acid, cyclosporine, tacrolimus, sirolimus and everolimus) for the pediatric patient population.

Endpoints will be population estimates of the pharmacokinetic parameters AUC, maximal concentration (Cmax), time to maximal concentration (Tmax), clearance (CL), volume of distribution (Vd) and elimination half-life (t1/2).

Study description

Background summary

Therapeutic drug monitoring (TDM) offers the possibility to individualize and improve a patient*s pharmacological treatment, based on the measurement of drug concentrations in biological samples. In clinical practice, TDM comprises the measurement of one or more drug concentrations associated with the administration of the dose of a certain drug. Dependent on the drug exposure measured, the dose of the drug may be increased or decreased. This is expected to result in a change in exposure, which in turn may yield more efficacy or less toxicity. In this way, the aim of TDM is to improve exposure aiming at maximizing efficacy and minimizing toxicity for an individual patient.

Conventionally, TDM is performed with blood or plasma obtained by venous blood sampling. This method is associated with several challenges such as i) the need for the patient to travel to the hospital or health center; ii) special conditions for sample transport to guarantee stability of the analyte and to decrease the biohazard risk; iii) sampling times not always representing the preferable peak or trough concentrations; iv) the method being invasive and v) delay of the outcome of the analyses with regard to the outpatient visit.
The Dried Blood Spot (DBS) may offer a solution for all these challenges. To perform the DBS technique, only a small amount of blood is needed and this sample can easily be obtained via a finger prick is put on a piece of filter paper, can be taken at home and is sent to the laboratory by post mail. Patients or their caregivers can perform the sampling at the appropriate time in the concentration curve, e.g. at the time of the trough concentration, while avoiding an extra visit to the hospital or health center. When arriving at the

hospital for a meet-up with the physician, adaptation of the dose based on the already available drug concentration is directly possible and a delay introduced by conventional sampling procedures is thereby avoided.

The majority of the patients on antifungal and immunosuppressive agents are treated at home, for very long periods, which is an obstacle to continuous monitoring of drug exposure. After solid organ transplantation, patients are required to take life-long immunosuppressive agents. Therapy with antifungal agents requires weeks but usually several months. It is important to monitor and protect this vulnerable population from start of therapy onwards, as not reaching target concentrations is associated with higher mortality.
DBS is thought to offer benefits over plasma venous sampling for TDM. The main purpose of the PROTECT (Personalized treatment of immunosuppressive and antifungal drugs through continuous home based monitoring with Dried Blood Spot sampling techniques in pediatric patients) study is to improve therapeutic management and patient participation in pediatric patients treated with antifungal and immunosuppressive agents. PROTECT is mainly financed by a ZonMW grant *Goed Gebruik Geneesmiddelen*.
Four patient organizations are actively involved in the PROTECT study, i.e. Nierpatiënten Vereniging Nederland (NVN), Vereniging voor zeldzame en genetische aandoeningen (VSOP), Vereniging ouders, kinderen en kanker (VOKK) and Stichting voor Afweerstoornissen (SAS).

Study objective

Primairy
To clinically validate a finger prick DBS method compared to conventional venous sampling for the analysis of 5 immunosuppressive and 4 azole antifungal drugs in the pediatric population.

Secondairy
• Feasibility of the novel finger prick DBS method in the pediatric population will be assessed. This includes scoring of relevant characteristics (attributes) of blood drawing methods for TDM, evaluation of the experience and attitude of both patients and parents regarding finger prick DBS sampling and evaluation of the understanding of the written instructions provided for performing the finger prick at home. The data obtained in this validation study will be used for the implementation of the DBS in therapeutic drug monitoring (TDM) being a less invasive procedure, and as a base for a discrete choice-experiment as part of the HTA.
• To design an inventory of types of costs that will be incurred in the process of DBS-based and conventional TDM as a preparation step for later health economic analysis.
• Data from this study will be used to construct a population pharmacokinetic model to optimize dosing and design new guidelines.

Study design

This is an observational multi-centre study in which DBS sampling is compared with conventional sampling for TDM in a steady state situation.

Study burden and risks

As in this study no change in therapy is performed it possesses a minimal risk. The risks associated with a finger prick are pain at the puncture site and risk of bleeding. The risks associated with venous blood sampling are similar (e.g., risk of infection, risk of hematomas and pain and/or discomfort at the puncture site). For inpatients: only patients with a venous catheter can participate. For outpatients: only patients who have their blood drawn for regular patient care will be included, with one one moment of blood drawing. In addition, only experienced personnel will perform the study.

This study focuses on those immunosuppressive agents and azole antifungals that are currently subject of TDM and most used in the pediatric population. As children are not small adults, unexpected findings are possible to arise, warranting validation in this target population. As to factors that are known to influence the outcome of the measurement through DBS by means of a finger prick, hematocrit is of particular relevance, and this parameter was shown to be different and more variable in the pediatric population. This has been recognized by other groups too and experts in the field emphasize the need for clinical validation in the target population. In the neonatal setting, various clinical validations for analysis of DBS have been performed, e.g. Suyagh et al. (2010) performed a validation of metronidazole in premature neonates by means of heel prick DBS.
Clearly, information on feasibility of DBS sampling in children and on costs relevant to DBS sampling in children can only be obtained through actual sampling in children.
The four involved patient organizations support the PROTECT proposal and underline the need for this novel sampling method especially in the pediatric population.

Contacts

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Selecteer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

• Patients aged between 2 and 18 years
• Admitted to the pediatric ward or visiting the doctor on an outpatient basis
• Having a venous catheter or blood is drawn for regular patient care
• Treated with at least 1 of the 9 drugs of interest
• Signed informed consent

Exclusion criteria

• Parents and/or patients are not able to understand the Dutch language

Study design

Design

Study type:	Observational invasive
Intervention model:	Other

Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-05-2015
Enrollment:	126
Type:	Actual

Ethics review

Approved WMO Date:	24-11-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-01-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
ClinicalTrials.gov	NCT02329808
CCMO	NL50382.091.14

Study results

Date completed:	03-12-2021
Actual enrolment:	89