Monitoring Adherence to Antihypertensive Drug Treatment by using a Dried Blood Spot test-test validation

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Primary Objective: to validate the measurement of drug levels of eight antihypertensive drugs in DBS against their corresponding plasma concentrationsSecondary Objective:to study the trough levels to assess expected range of drug levels at a random...

Ethical review	Approved WMO
Status	Pending
Health condition type	Vascular hypertensive disorders
Study type	Observational invasive

Summary

ID

NL-OMON46253

Source
ToetsingOnline

Brief title
Antihypertensive drugs in DBS-validation

Condition

- Vascular hypertensive disorders

Synonym
high blood pressure, Hypertension

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: Adherence, Hypertension, Therapeutic drug monitoring

Outcome measures

Primary outcome

Agreement of plasma levels of eight hypertensive drugs when measured in DBS

compared to plasma levels obtained by venipuncture

Secondary outcome

Plasma concentrations of eight hypertensive drugs 1-4 hours after intake

Trough levels of eight antihypertensive drugs

Study description

Background summary

Resistant hypertension, defined as uncontrolled blood pressure despite concurrent use of three antihypertensive drugs including a diuretic is a common health issue leading to costs and suboptimal cardiovascular prevention. Around 12% of patients with hypertension fulfill this definition.(1) A major part of these patients (estimated 40-60%) considered to be *therapy-resistant* have a problem in adherence to their diet and intake of their medication explaining their assumed resistance to therapy.(2) To distinguish these individuals from those with secondary causes of hypertension or *true* therapy-resistant patients can be difficult. Current practice when non-adherence is suspected to be the cause of resistant hypertension is hospitalization for at least half a day for supervised intake of prescribed medication.(3) This is costly, time-consuming and even in supervised intake it is not certain that the patient did swallow the given drug.
Measurement of serum or urine levels of antihypertensive drugs by liquid chromatography-mass spectrometry (LC-MS) has been performed for research purposes but is not yet endorsed for use in clinical practice.(4, 5) Measuring drug levels has become available in dried blood spots (DBS) which can be easily obtained by a finger prick.(6-8) Due to this convenient and patient-friendly sampling method, this technique is becoming more and more popular in therapeutic drug monitoring (TDM) and is most commonly used in organ

transplantation and psychiatry. In hypertension, using DBS enables immediate sampling in the office when suspecting non-adherence or during a sitting automatic (*datascope*) or 24 hours ambulatory blood pressure measurement (24h ABPM) without an additional visit to the laboratory.(6)

In short, blood is obtained by a finger prick and applied to a piece of filter paper on a *DBS card* where it can dry. In the laboratory, this dried blood spot is punched out, extracted and further analyzed using liquid chromatography-mass spectrometry (LC-MS). We are currently developing this test for the most commonly used antihypertensive drugs of four different classes. Also some active metabolites are measured, they are mentioned between brackets:
-angiotensin converting enzyme (ACE) inhibitors: enalapril (enalapril-d5 maleate) and perindopril
-angiotensin II receptor blockers (ARB): losartan (losartan carboxylic acid) and valsartan
-diuretics: hydrochlorothiazide and spironolactone (canrenone)
-calcium channel blockers: amlodipine and nifedipine

The method will be validated according to the guideline on bioanalytical methods of the European Medicine Agency.(9) Different concentrations of the different drugs and metabolites will be added to drug-free blood from blood donors. These samples will be used to define selectivity, calibration curves, the lower limit of quantification, accuracy, precision, dilution integrity, recovery, stability, carry-over and the matrix effect including effects of different hematocrit levels.
The current study is necessary to validate the developed method in patients before further use in research and clinic. To ascertain measurable drug levels, we will select patients expected to be adherent based on blood pressure levels below target. The next step will be a trial in patients with resistant hypertension to assess (non-)adherence and study the effect of feedback on drug levels on adherence and as a consequence reaching blood pressure targets. For this study, we recently received a ZonMW Grant (Rational Pharmacotherapy)

Study objective

Primary Objective:
to validate the measurement of drug levels of eight antihypertensive drugs in DBS against their corresponding plasma concentrations
Secondary Objective:
to study the trough levels to assess expected range of drug levels at a random time point

Study design

Cross-sectional study needed for validation of a newly developed test.

Patients will be asked to undergo a finger prick to obtain a dried blood spot (DBS) at the day they undergo automatic 45-minutes blood pressure measurement. This is usually a couple of weeks before their visit to the physician. Usually, also blood is taken on this day. We will ask for an extra tube. Half of the patients will be asked to not take the measured drug in the morning (trough level) while the other half wil be measured after drug intake in the morning (peak level)

Study burden and risks

The risk and burden is limited to the risk and burden of venipuncture and a finger prick . This is the same risk they will also have at regular blood sampling or undergoing 24h ABPM. The risk of venipuncture is very low and mainly exists of syncope, bleeding complications or formation a pseudoaneurysm. At the day of the trough level, the studied medication will be taken slightly later than normally. We will only select patients visiting their physician in the morning. This will have no direct negative consequences when the drugs will be taken right after the venipuncture.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Automated blood pressure measurement (datascope) or office blood pressure <135/85 mm Hg
Usage of at least one antihypertensive drug for which the DBS-test has been developed

Exclusion criteria

Insufficient understanding of Dutch

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	16-10-2017
Enrollment:	100
Type:	Anticipated

Ethics review

Approved WMO

Date:	24-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2017
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

No registrations found.

In other registers

Register	ID
CCMO	NL57006.078.16