Grasping the Underlying Mechanisms of drug Disposition and Receptor Occupancy by Positron-emission tomography Studies (GUMDROPS): A feasibility study for the use of 11C-telmisartan to quantify individual differences in target-site exposure in diabetes patients;

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Primary objectives:* To assess telmisartan target (i.e. receptor) specific binding in vivo* To assess receptor occupancy of telmisartan in vivo* To determine optimal scanning time in vivoSecondary objective:* To explore the effect of telmisartan on...

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

Summary

ID

NL-OMON46612

Source
ToetsingOnline

Brief title
GUMDROPS

Condition

- Diabetic complications

Synonym
Diabetes

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: European Federation for the Study of Diabetes

Intervention

Keyword: drug disposition, Positron Emission tomography, receptor occupancy, telmisartan

Outcome measures

Primary outcome

The main study parameters are dynamic PET data and images and radiation count

measurement, and free plasma concentrations of telmisartan and its metabolite

telmisartan-glucoronide.

Secondary outcome

The secondary study parameters are GFR and UACR.

Study description

Background summary

In clinical research as well as in clinical practice identical therapy is prescribed for all patients. This one-size-fits-all approach may not be optimal, as it is known that the response to a drug varies between individuals. Furthermore, we have shown that many drugs used in patients with diabetes affect multiple cardiovascular/renal risk markers. Again changes in these risk markers vary between individuals. The mean group results of randomized controlled trials guide clinical decision making, whereas the individual variable effects of many drugs in multiple parameters far exceeds the mean drug effects on a population level. This provides a clear rationale to pay more attention to studying the individual and to explore the underlying mechanisms

in drug responsiveness in order to tailor optimal therapy for each individual and unravel determinants of therapy resistance. The ultimate aim of this study is to determine the underlying mechanisms and determinants of the variability in drug response. This will lead to the identification of previously unknown factors that determine therapy response and provide the potential to improve the treatment of microvascular complications of type 2 diabetes in the future. We hypothesize that the underlying mechanisms of the varying response in multiple parameters within an individual can be attributed to variability in the causal path between drug administration, drug tissue distribution, and tissue receptor interaction. To test this hypothesis we have synthesized an 11C PET radiotracer of the ARB telmisartan, retaining the original molecular structure. This drug class was selected for several reasons. First, it represents an established renal protective drug class and it is likely that in the near future telmisartan will form the guideline recommended therapy for diabetic kidney disease. Importantly, we have shown for ARB that these drugs have effects on multiple renal risk markers and that individual patients show a huge variability in response in these multiple renal risk markers (Schievink et al. 2015). The radiotracer we use, 11C-telmisartan, is structurally identical to the original compound and pharmacodynamic properties are therefore not changed. The safety and feasibility of 11C-telmisartan has been shown in healthy volunteers (Shimizu et al. 2012), although that study did not specifically calculate an input function and specific binding of the tracer. In this clinical feasibility study we will assess 11C-telmisartan pharmacokinetic characteristics and determine specific receptor binding, receptor occupancy and optimal scanning time in 9 selected patients with diabetes and urinary albumin:creatinine ratio (UACR) >1.7 mg/mmol.

Study objective

Primary objectives:
* To assess telmisartan target (i.e. receptor) specific binding in vivo
* To assess receptor occupancy of telmisartan in vivo
* To determine optimal scanning time in vivo
Secondary objective:
* To explore the effect of telmisartan on estimated Glomerular filtration Rate (GFR)
* To explore the effect of telmisartan on Urinary Albumin-creatinine ratio (UACR)
* To explore differences in drug disposition between UACR-responders and -non-responders to telmisartan

Study design

A randomized open label feasibility study will be conducted in subjects with Type II diabetes and UACR >1.7 mg/mmol. The study will consist of a screening visit, a 4-week run-in phase for subjects on ACEi/ARB treatment and 2 treatment

days.
On the first study day, after IV radiotracer administration, a baseline dynamic PET scan will be taken to measure selective uptake and accumulation in the region of interest (ROI; kidney, aorta and part of the liver). On the second study day, after 20, 80 or 120 mg oral telmisartan administration, a second IV radiotracer dose will be administered followed by a second 90-minute dynamic PET scan (post-drug). In this second scan, receptor binding sites are occupied by telmisartan, hence the reduction of radiotracer uptake compared to the baseline scan can be used to determine the receptor occupancy based on the binding potentials obtained from both scans. In all patients arterial plasma samples will be taken after radiotracer administration, to quantify radiation measure and free plasma concentrations of telmisartan and its metabolite telmisartan-glucoronide.

Study burden and risks

Patients will be subjected to physical examination by the principal investigator or delegate before inclusion. This physical examination entails a routine investigation of heart, lungs and abdomen. A pregnancy test will be performed in female participants of the study. Blood pressure will be monitored during screening and on both study days. Body weight will be measured during screening and first study day.

On the first study day, a CT topogram will be performed to optimally position the individual patient for the dynamic PET scan, e.g. with the kidney, aorta and part of the liver inside the field of view. At time=0 hours, patients will receive an intravenous (IV) diagnostic dose of 11C-telmisartan radiotracer followed by a 90-minute dynamic PET scan (Shimizu et al. 2012). On the second study day, a CT topogram will be performed to optimally position the individual patient for the dynamic PET scan, and three dose groups will receive an oral dose of 20, 80 or 120 mg telmisartan, respectively, at t=0 hours. At the approximate time of maximal plasma telmisartan concentration (tmax, 1h) a second IV radiotracer dose will be administered immediately followed by a second 90-minute dynamic PET scan.

Patients are asked to collect their first morning urine void at three days before day of screening for measurement of albuminuria. During the two treatment periods, 24-hour urine will be collected.

At screening and on both study days (prior to dosing) a blood sample will be drawn by venepuncture for laboratory measurement (10 mL each). During the two study days, in all patients, arterial plasma samples (10 samples of ~50 microlitre) will be taken after radiotracer administration, to quantify radiation measure of 11C-telmisartan and its metabolite 11C-telmisartan-glucoronide. For this procedure (after positive hand functionality test)an anaesthesiologist will place an arterial cannula under

local lidocain anaesthesia. Also, on the second study day, plasma samples (10 samples of 4 mL) will be taken to quantify unlabelled plasma concentrations of telmisartan and its metabolite telmisartan-glucoronide for the purpose of determining the pharmacokinetic parameters (e.g clearance and volume of distribution) for each subject. Over the entire duration of the study, approximately 23 samples will be taken per subject, totalling up to 71 mL blood.

There is no direct benefit to the patient*s health be expected from this study. Participation in the study is on a free-will base. Patients will receive restitution of all costs of transportation. Patients will not receive priority for treatment of other diseases in the clinic during this study. Participation in the proposed study is accompanied with only minor risks, if any at all.

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

Main inclusion criteria are;
- Type 2 diabetes
- urinary albumin:creatinine ratio (UACR)> 1.7 mg/mmol
- Age * 45 years * 70 years
- Written informed consent

Exclusion criteria

Main exclusion criteria are;
- Pregnant women and women of child-bearing potential who are not using reliable contraception;
- Cardiovascular disease: myocardial infarction, angina pectoris, percutanous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, heart failure (NYHA I-IV) < 6 months before inclusion;
- History of renal artery stenosis;
- History of hypersensitivity to telmisartan;
- History of autonomic dysfunction (e.g. history of fainting or clinically significant orthostatic hypotension);
- Uncontrolled blood pressure (office blood pressure * 160/ 100 mmHg);
- Participation in any clinical investigation within 3 months prior to initial dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.;
- Donation or loss of 400 ml or more of blood within 8 weeks prior to initial dosing;
- History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of drug or alcohol abuse as indicated by the laboratory assays conducted during the screening;
- Lithium use;
- Any medication, surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of medications including, but not limited to any of the following:;
o Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
o Gastro-intestinal ulcers and/or gastrointestinal or rectal bleeding within last six months;
o Pancreatic injury or pancreatitis within the last six months;
o Evidence of hepatic disease as determined by any one of the following: ALT or AST values exceeding 3x ULN at inclusion visit, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt;

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2019
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	11C-telmisartan
Generic name:	11C-Telmisartan
Product type:	Medicine
Brand name:	Micardis
Generic name:	Telmisartan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-12-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	30-04-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	11-11-2019
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2017-004236-11-NL
CCMO	NL63683.042.17