Grasping the Underlying Mechanisms of drug Disposition and Receptor Occupancy by Positron-emission tomography Studies (GUMDROPS)

Gepubliceerd: 14-11-2017 Laatst bijgewerkt: 13-12-2022

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Ethische beoordeling	Niet van toepassing
Status	Anders
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON20821

Bron
NTR

Verkorte titel
GUMDROPS

Aandoening

Type II Diabetes Mellitus and and microvascular complications

Ondersteuning

Primaire sponsor: University Medical Center Groningen
Overige ondersteuning: European Federation for the Study of Diabetes

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The main study parameters are dynamic PET data and images and radiation count measurement, and free plasma concentrations of telmisartan.

Toelichting onderzoek

Achtergrond van het onderzoek

Intervention in the renin-angiotensin-aldosterone-system is a cornerstone treatment to slow renal function decline in diabetes. Accordingly, the guideline suggests that all patients should be treated with an Angiotensin-Converting-Enzym-inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB). Yet, a significant proportion of patients does not respond to ACEi or ARB therapy both in terms of its surrogates like albuminuria and hard renal outcomes. Consequently, a considerable proportion of patients remain at high risk of progressive renal function loss. We hypothesize that the variability in drug response between individuals is the result of between individual variability in drug disposition to target tissues. To test this hypothesis we have synthesized an 11C PET radiotracer of the ARB telmisartan, retaining the original molecular structure. As a first step, we will evaluate 11C-telmisartan receptor specific binding, receptor occupancy, and optimal PET scanning time. As such, in this clinical feasibility study, we will generate essential PET data to optimize the design of a future clinical study in patients with type 2 diabetes and microvascular complications.

Doel van het onderzoek

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.

In this clinical feasibility study we will assess radiolabeled telmisartan pharmacokinetic characteristics and determine specific receptor binding, receptor occupancy and optimal scanning time in patients with diabetes and microvascular complications. The main objectives are;

To assess telmisartan target (i.e. receptor) specific binding in vivo

To assess receptor occupancy of telmisartan in vivo

Onderzoeksopzet

During the study day, for all patients, after radiotracer drug administration, arterial plasma

samples will be taken obtained by an automated sampler for radioactivity in full blood and plasma. After administration of oral telmisartan 10 venous blood samples will be obtained for telmisartan PK assessment. 24-hour urine will be collected for the measurement of 24-h protein, albumin, sodium, potassium, creatinine, and urea excretion.

Onderzoeksproduct en/of interventie

On the study day, a non-diagnostic dose CT scan will be performed to optimally position the individual patient for the dynamic PET scan (e.g. with kidney, aorta and part of the liver inside the field of view) and attenuation correction, respectively. At time=0, patients will receive an intravenous diagnostic dose of 400Mbq 11Ctelmisartan radiotracer followed by a 90-minute dynamic PET scan. Then, three dose groups will receive an oral dose of 20, 80 or 120 mg telmisartan, respectively at t=3h. At the approximate time of maximal plasma telmisartan concentration (tmax, t=4h) a second intravenous radiotracer dose will be administered immediately followed by a second 90-minute dynamic PET scan. 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 venous blood samples will be taken after oral telmisartan administration to obtain plasma concentrations of telmisartan.

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- Type 2 diabetes

- urinary albumin:creatinine ratio (UACR) >3.4 mg/mmol

- Age ≥ 40 years <70 years

- Written informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Pregnant women and women of child-bearing potential who are not using reliable contraception

- Use of an ACE inhibitor or angiotensine receptor blocker

- 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)

- Active malignancy

- History of autonomic dysfunction (e.g. history of fainting or clinically significant orthostatic hypotension)

- 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 such

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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Anders
(Verwachte) startdatum:	01-01-2018
Aantal proefpersonen:	9
Type:	Onbekend

Ethische beoordeling

Niet van toepassing

Soort:	Niet van toepassing

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL6637
NTR-old	NTR6823
Ander register	2017-004236-11 : 201700716

Resultaten