Inhibition of salivary glands to reduce uptake and toxicity of PSMA-ligands

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To determine if inhibition with GPB can provide a significant reduction in the accumulation of systemically administered Ga-PSMA in salivary glands on PET/CT, with the aim to determine if GPB can prevent toxicity from Lu-PSMA or other...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Salivary gland conditions
Study type	Interventional

Summary

ID

NL-OMON46014

Source
ToetsingOnline

Brief title
Inhibition of Salivary Glands

Condition

- Salivary gland conditions

Synonym
accumulation in salivary glands., Biodistribution of PSMA-ligands

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: KWF

Intervention

Keyword: Glycopyrronium bromide, Prostate cancer, PSMA-ligand, Salivary glands

Outcome measures

Primary outcome

The total uptake of Ga-PSMA on PET/CT in all macroscopic salivary glands

together (and its relative decrease after inhibition with GPB).

Secondary outcome

The total perfusion signal on ASL MR in representative thick slices of the

parotid and submandibular glands together (and its relative decrease after

inhibition with GPB).

Study description

Background summary

Many pharmaceuticals can damage salivary glands, and this can lead to a dry mouth (xerostomia) with detrimental effect on quality of life. Systemically administered pharmaceuticals reach the salivary glands via blood supply and diffusion, and their accumulation can be further augmented by active or passive transporters. This mechanism also applies to radiopharmaceuticals used in radionuclide therapy (RNT). Radiolabelled ligands to the prostate-specific membrane antigen (PSMA) are increasingly used to treat metastatic prostate cancer. The currently applied Lutetium-177-PSMA-617 ligand (Lu-PSMA) shows very high uptake in salivary glands, which is explained by the high perfusion of salivary glands and the abundant expression of the PSMA receptor on their acinar and ductal seromucous cells. As a result, salivary glands are inadvertently exposed to high radiation doses in Lu-PSMA treatment, with xerostomia as a known dose-limiting factor. Other pharmaceutical treatments with potentially significant salivary gland toxicity include RNT with Iodine-131 and various chemotherapies (often in combination with external beam radiotherapy).
Salivation can be inhibited with anticholinergic / antimuscarinergic pharmaceuticals that target the sympatic and parasympatic nerve systems. Glycopyrronium bromide (GPB) inhibits salivary glands and induces vasoconstriction in afferent vasculature via antagonizing the muscarine

receptor subtype 3 (M3) and to a lesser extent subtype 2 (M2). Intravenous administration of 0.2mg GPB results in a temporary reduction in salivation to about 25%, that lasts for a few hours and recovers in the course of 6-8 hours. Central effects hardly occur since it does not cross the blood-brain barrier. Temporary peripheral side effects have been described (e.g. vomiting, constipation, urine retention, tachycardia and flushes), however with a single dose of 0.2mg the incidence and extent of peripheral side effects is limited.
The hypothesis is that inhibition with GPB during the biodistribution phase of toxic pharmaceuticals leads to reduced delivery to and accumulation in salivary glands, consequentially resulting in less toxicity. The uptake of PSMA-ligands can be assessed with quantitative PET/CT imaging using the diagnostic radiopharmaceutical Gallium-68-PSMA (Ga-PSMA). A reduction in Ga-PSMA uptake in salivary glands achieved by GPB will predict a similar protective effect for treatment with Lu-PSMA, and potentially for treatments with other systemically administered pharmaceuticals.
A secondary hypothesis is that suppressed local perfusion in salivary glands is the main effector mechanism in the anticipated reduction of pharmaceutical uptake by GPB. Reductions in local perfusion can be assessed using quantitative arterial spin labelling magnetic resonance (ASL MR) imaging. This technique allows continuous sampling of perfusion parameters in vivo, without a need for administration of intravenous contrast and thus without toxicity.

Study objective

To determine if inhibition with GPB can provide a significant reduction in the accumulation of systemically administered Ga-PSMA in salivary glands on PET/CT, with the aim to determine if GPB can prevent toxicity from Lu-PSMA or other pharmaceuticals. Perfusion will be measured to determine if ASL MRI provides a measurable signal for application in subsequent studies.

Study design

Prospective interventional phase II study.

Intervention

Intravenous administration of the investigational product GPB.

Study burden and risks

Participating patients will visit the hospital for 1 extra day, for a single administration of GPB by IV canula, a single PSMA PET/CT including tracer administration by the same IV canula, and (optional) 2 x ASL MR of the neck without contrast fluid. In addition, patients will experience temporary signs of the effect of GPB, including the feeling of a dry mouth or skin, which will

disappear after an average of 8 hours.

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

- Received PSMA PET/CT on clinical indication (<1 month before study date).
- At least one PSMA-positive tumour location visible with diameter >1cm.

Exclusion criteria

- Poor quality of the baseline PSMA PET/CT scan
- Planned start or changes in treatment prior to study procedures.

- Age < 18y
- Inability to provide informed consent
- History of disease or treatment involving the salivary glands
- Currently on neurotransmitter blocking/stimulating medication
- Contra-indications for anticholinergic medication, including glaucoma, obstruction of digestive or urological tract, megacolon, ileus, tardive dyskinesia
- (For optional MR-scans only): Standard contra-indications for MR

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-05-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Robinul for injection (Biosyn artzneimittel GmbH)
Generic name:	Glycopyrronium bromide

Ethics review

Approved WMO

Date:	24-05-2018
Application type:	First submission

Review commission: METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2018-001372-37-NL
CCMO	NL65680.031.18