The effect of dexamethasone on the biodistribution of [3-N-11C-methyl]temozolomide in glioblastoma multiforme patients

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(1) Determination of the effect of dexamethasone on the biodistribution and kinetics of [11C]TMZ in GBM patients. (2) The effect of DXM on CBF. If there is an effect of DXM on CBF: (3) The effect of blood flow in the brain on [11C]TMZ uptake.

Ethical review	Approved WMO
Status	Pending
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON37565

Source
ToetsingOnline

Brief title
Effect of dexamethasone on the biodistribution of [11C]temozolomide

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
glioblastoma multiforme and malignant brain tumor

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: biodistribution, dexamethasone, glioblastoma, temozolomide

Outcome measures

Primary outcome

The influence of dexamethasone on the biodistribution of [11C]TMZ in the brain.

Secondary outcome

1) To assess plasma kinetics of [11C]TMZ in humans, including assessment of the presence of radioactive metabolites.

2) To study the effect of DXM on CBF.

3) If there is an effect of DXM on CBF, we will study the relation between changes in CBF and [11C]TMZ uptake in the brain and especially in the brain tumor.

Study description

Background summary

Radiotherapy and temozolomide (TMZ) are expected to be the backbone of treatment for patients with glioblastoma multiforme (GBM), and possibly also for patients with other glioma subtypes, during the next decade(s). Apart from (chemo-)irradiation and adjuvant courses of TMZ, the majority of glioma patients are treated with corticosteroids in order to avoid peritumoral edema, and approximately half of the patients are on anti-epileptic drugs (AED), such as levetiracetam.
Although interactions with other drugs are suspected to affect the efficacy of TMZ, hardly any quantitative data on this issue are available. Corticosteroids, such as DXM, are thought to affect the levels of other drugs in the brain,

including TMZ, for example by causing a dramatic decrease in blood-tumor barrier permeability. Secondly, DXM influences transcellular and paracellular pathways that regulate transport of drugs over the blood-brain tumor barrier. Thirdly, DXM increases P-glycoprotein- (P-gp) and breast cancer resistance associated protein (BCRP)-mediated drug efflux activity in the blood-brain barrier (BBB). A variety of cytostatic agents and many AEDs are substrates for P-gp. Thus, interactions between TMZ, corticosteroids and AEDs at the P-gp level may affect TMZ concentration in the brain and in glioma tumor tissue, which may hamper its efficacy. Increased knowledge on the biodistribution of TMZ will improve treatment by allowing to adjust TMZ dosage when, for example, corticosteroids are prescribed.
Positron Emission Tomography (PET) offers an excellent opportunity to determine biodistribution and pharmacokinetics of drugs such as TMZ, and for that reason, PET is the ideal instrument to quantify the effects of co-medication, e.g. DXM. Previous studies have demonstrated that PET-scanning of [3-N-11C-methyl]temozolomide ([11C]TMZ) is a robust tool to analyse and predict tissue drug concentrations in order to determine the most rational dosing schedules of TMZ. When we will be able to visualize and quantify the effects of corticosteroids on [11C]TMZ kinetics in GBM, this may contribute to the optimalization of treatment schedules.
Furthermore, it is also important to assess the effect of DXM on the cerebral blood flow (CBF), as studies on the effect of DXM on CBF have, so far, been inconclusive.

Study objective

(1) Determination of the effect of dexamethasone on the biodistribution and kinetics of [11C]TMZ in GBM patients. (2) The effect of DXM on CBF. If there is an effect of DXM on CBF: (3) The effect of blood flow in the brain on [11C]TMZ uptake.

Study design

Single-centre proof of concept / feasibility study in humans.

Intervention

One gift of 10mg dexamethasone between morning- and afternoon scanning session.

Study burden and risks

1) Radiation exposure
The radiation exposure of 1100 MBq [15O] H2O is approximately 0.5 mSv. The radiation exposure of 370 MBq of [11C]TMZ is approximately 1.4 mSv. The radiation exposure of a low-dose CT of the head is 0.25mSv. Therefore, each patient will receive a total radiation dose of 4.3 mSv, which is below the

general accepted amount of radiation burden of 10 mSv. For comparison, the natural background radiation dose in the Netherlands gives annual dose of 2 - 2.5 mSv.

2) Idiosyncratic reaction to the tracer
The injected mass of [11C]TMZ in this study is negligible. Side effects have never been reported at tracer doses used in PET studies. Since the molecular structure of [11C]TMZ is exactly the same as the molecular structure of the drug TMZ (see IMPD of [11C]TMZ), pharmacology and pharmacokinetics are comparable (see IB of TMZ). Subjects have already been treated with (chemo-)irradiation and receive or have received adjuvant TMZ when included in this study without major side-effects. Thus, the [11C]TMZ will certainly be negligible compared to treatment doses. A physician will be present during PET scanning.

3) Adverse events from a single gift of DXM
Most of the adverse events mentioned in the SPC of DXM are associated with repeated doses and long-term use of DXM. The risk of adverse events from a single gift of 10mg of DXM i.v. are low, and the occurrence of for example insomnia or psychiatric disturbances, such as depression or psychoses is rare. Furthermore, it is possible to have a hypersensitivity reaction after a single gift of DXM. However, most participants have used DXM previously, for clinical reasons, without experiencing hypersensitivity reaction. The chance of developing such a response when using DXM (again) is negligible. Patients with a history of hypersensitivity reaction to DXM will be excluded. If patients do experience hypersensitivity reaction on DXM, 2mg tavegil (in 10 ml NaCl 0.9) will be administered. A physician will constantly be present during the injection of DXM and the PET scan procedure.

4) Intravenous and intra-arterial cannulation
There is a very small risk of infection and bleeding associated with intravenous and intra-arterial catheters, which are prevented by proper techniques.

5) Blood sampling.
Adverse effects of blood sampling will be minimised by exclusion of subjects with low haemoglobin levels (Hb must be > 8 mmol / litre at the time of the scan for males and be > 7,5 mmol / litre for females). No more than 300 ml blood will be withdrawn during the total PET procedure and screening.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HZ
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histopathological confirmed diagnosis of GBM
- Remainder of tumor on post-irradiation follow-up MRI
- Age between 18-70 years
- Performance status Karnofsky index > 60
- Laboratory requirements:
- Platelets > 100 x 109/l
- Hb must be >8 mmol \ litre at the time of the screening for males and >7.5mmol \ litre for females
- Neutrophils > 1.5 x 109/L
- Liver- and kidney function: serum creatinine level < 1.5 times the upper limit of normal, liver function values <3 times the upper limit of normal
- No use of DXM (at time of participation to this study)

Exclusion criteria

- Any clinical significant abnormality of any clinical laboratory test, with the exception of the values mentioned above (for platelets, haemoglobin, neutrophils, kidney- and liver function)

- Any subject who has received any investigational medication within 30 days prior to the start of this study, or who is scheduled to receive an investigational drug
- Major psychiatric or neurological disorder other than GBM with or without epilepsy
- History of alcohol and/or drug abuse (DSM-IV criteria)
- History of coagulation problems
- Claustrophobia
- Abnormalities on MRI other than GBM (and related abnormalities such as edema) and/or abnormalities on MRI other than white matter changes or an incidental small lacunar lesion without clinical diagnosis
- Metal objects in or around the body (braces, pacemaker, metal fragments)
- Use of antithrombotics or ASA
- Use of drugs that are known to be P-gp substrates, other than AEDs
- Need for elective surgery <= 6 weeks
- Pregnancy or nursing mothers
- Unable to understand or read the Dutch language
- Any of the following contra-indication for DXM (see also SPC of DXM):
- Hypersensitivity to one of the active constituents or additives
- Ulcus ventriculi or ulcus duodeni
- Active infections: viral infections, systemic fungal infections, parasitic infections, tropical worm infections
- Recent vaccination with living weakened virus
- Anamnestic hypersensibility for sulphite
- History of glucocorticoid-induced myopathy
- Diabetes mellitus (type 1 or 2)

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2012
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	[3-N-11C-methyl]temozolomide
Generic name:	[3-N-11C-methyl]temozolomide
Product type:	Medicine
Brand name:	dexamethasone
Generic name:	dexamethasone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2011-005500-16-NL

Register	ID
CCMO	NL38760.029.11