The peripheral effects of prednisolone on glucose metabolism, metabolic hormones, insulin sensitivity and insulin secretion in healthy young males and males with metabolic syndrome * two randomized, placebo controlled, double blind, dose-response, parallel group intervention studies.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON31204

Source
ToetsingOnline

Brief title
PANTHEON-studies

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)

- Therapeutic and nontherapeutic effects (excl toxicity)

Synonym
metabolic effects of prednisolone; glucocorticoid-induced insulin resistance

Health condition

Metabole effecten van behandeling met prednisolon

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Het onderzoek wordt gefinancieerd vanuit 'Top Instituut Pharma (TIP)'. Zowel Top Instituut Pharma;als NV Organon als het VUmc zijn bij dit onderzoek als sponsor betrokken;en delen de kosten. (Voor meer informatie zie: www.tipharma.com).

Intervention

Keyword: Beta cell function, Diabetogenic side effects, Glucocorticoids, Insulin sensitivity

Outcome measures

Primary outcome

In PANTHEON-I, various aspects of beta-cell function will be studied after

intravenous (combined eu- and hyperglycemic clamp with subsequent arginine

stimulation) and orally (mixed-meal test) administered glucose.

In PANTHEON-II, GC-induced changes in hepatic and peripheral insulin

sensitivity and subsequent changes in intermediary metabolism/metabolic fluxes,

such as rate of endogenous glucose production, lipolysis and proteolysis, and

the underlying molecular mechanism, will be studied.

Secondary outcome

Secundary outcomes of PANTHEON-I:

1. circulating biomarkers (plasma)

2. Microvascular function

3. Blood pressure

4. Molecular mechanisms

Secundaire uitkomsten van PANTHEON-II betreffen de effecten van bovengenoemde

interventie met prednisolon op:

1. circulating biomarkers (plasma)

2. Body composition

3. Blood pressure

4. body fat distribution

5. Molecular mechanisms

Study description

Background summary

Glucocorticoids, such as prednisolone, are the most frequently prescribed anti-inflammatory and immunosuppressive medication. Although GCs display excellent efficacy in a great number of (auto-immune) diseases, the side-effect profile often limits their therapeutical benefit. Major side effects associated with GC treatment include changes in glucose, lipid and protein metabolism, leading amongst others, to insulin resistance, glucose intolerance, muscle wasting and dyslipidemia. The current development of *dissociated glucocorticoid receptor activators*, which seem to lack these deleterious effects, while preserving its immunomodulatory effects, and the recently identified role of cortisol in the development of the metabolic syndrome (MetS) and type 2 diabetes (T2DM) , have led to a renewed interest in the mechanisms of these diabetogenic effects.
In this Top Institute Pharma (TIP) study group is, in addition to cooperation between a number of pre-clinical and clinical groups, NV Organon involved, which is currently developing dissociated glucocorticoid receptor agonists.
The results of these trials may support the development of the above-named

compounds, which may become of great importance for the millions of people world-wide that require GC-treatment and who suffering daily from their dysmetabolic side effects.

Study objective

The objective of these studies is to identify the primary mechanisms of GC-induced dysmetabolic effects in humans and to find biomarkers that reflect these side effects of GC treatment and which can be followed during therapy and in future clinical trials.

Study design

The PANTHEON studies are randomized, placebo controlled, dubbel-blind, dose-response, parallelgroup intervention studies.
It concerns a monocenter studie (VUmc) and in total 124 participants will be included.

32 Healthy males in PANTHEON-I
32 Subjects with the metabolic syndrome in PANTHEON-I
30 Healthy males in PANTHEON-II
30 Subjects with the metabolic syndrome in PANTHEON-II

Intervention

Participants will be randomized to one of the following groups: placebo, prednisolone 7.5 mg/daily or prednisolone 30 mg /daily.
Treatment duration is 14 days.

Study burden and risks

We are well aware of the possible demand that may be imposed on the participants. Overall, participants will travel 7 times to the study location. The duration of these visits ranges between 30 minutes (control visit) and 8hours (stable isotope test). A total amount of 500 mL blood will be withdrawn in both PANTHEON-I and PANTHEON-II.
nomen. The maximum amount of blood to be collected during one visit is 130 mL. All possible measures will be taken to minimize the discomfort for the participants. During the clamps, meal tests and stable isotopes tests, patients will assume a semirecumbent position, to alleviate discomfort, and will be allowed to read or watch TV/video. Following the tests, all participants will be presented with a meal and coffee/tea. During the clamps (a restricted regimen of) water intake is allowed. Subjects with claustrophobia are excluded from MRI-scans. The amount of radiation used during a DEXA-scan is 1/10 of a standard CXR. Lidocaine will be used as a local anesthetic during the biopsy procedures. Pressure bandages will be used to reduce the change of the

development of a hematoma. Our current experience indicates that no harm is being done by performing these biopsies and that the small incision heals very quickly. The medication in this study, prednisolone, is a regular orally administered pharmacological compound, registered for the treatment of a wide range of (auto-immune) diseases. Since prednisolone has been used extensively, its potential, clinically relevant side-effects are well documented. Aside from the development of transient impairment of insulin sensitivity and subsequent short-lived metabolic adaptations (i.e. our study goals), we do not expect to find other adverse effects in our short treatment period with low- to medium-doses of prednisolone. In a recent study in healthy males, using an identical intervention as in our study, it was shown that GC-induced insulin resistance was quickly resolved after cessation of therapy. Glucose levels were not changed during the study, and the increased levels of C-peptide and pro-insulin (signs of insulin resistance) had returned to baseline after one-week of follow-up. Furthermore, no participants had to discontinue the study due to health problems, and no serious adverse events were reported (NV Organon, unpublished data).

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

For all participants:
1. signed informed consent
2. caucasian male
3. normal day-and night rythm
For healthy volunteers:
1. Good health (from history, physical exams, blood tests)
2. fasting glucose < 5.6 mmol/L
3. 20 < BMI< 25.
4. 20 < age < 55 jaar.
For subjects with the metabolic syndrome:
1. metabolic syndrome (according to IDF criteria). Waist > 93 cm and at least 3 of the following criteria:
- triglycerides > 1.7 mmol/L
- HDL cholesterol < 1.03 mmol/L
- blood pressure > 130/85 mmHg
- disturbed glucose tolerance (definded as: fasting glucose between 5.6 en 6.1 mmol/L en 2 hr plasma glucose after oral glucose tolerance test < 11.0 mmol/L).

Exclusion criteria

For all participants:
1. allergy for prednisolone
2. any other contra-indication for prednisolone use.
3. use of glucocorticoids in the past 3 months
4. Recent participation in a clinical trial
5. Blood donation in the past 3 months
6. (history of) alcohol or drugs abuse.
7. Not willing or able to sign the informed consent or not being able to understand the study information
8. smoking
for healthy males:
1. any present disorder
2. any medication use, except for incidental use of analgesic agents
3. 1ste degree relative with type 2 diabetes
4. intensive physical activity (sport) > 2x/week.
For males with the metabolic syndrome:

1. serious (pulmonary, liver, kidney) diseases
2. history of cardiovascular disease (such as MI or CVA)
3. psychiatric disorder
4. depression
5. any condition that interferes with the HPA axis
6. malignancy
7. other condition or usage of medication that may interfere with study endpoints of hypothesis. Eligibility will be assessed in each individual case by the research physician and internist.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-11-2007
Enrollment:	124
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Prednisolon
Generic name:	Prednisolon
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-08-2007
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	EUCTR2007-002597-57-NL
Other	ISRTCN78149983 (PANTHEON-I) en ISRTCN83991850 (PANTHEON-II)
CCMO	NL17711.029.07