Recovery of circadian rhythm of the hypothalamic-pituitary-adrenal axis during glucocorticoid tapering in ANCA-associated vasculitis, a pilot study

Published: 07-08-2014
Last updated: 15-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Adrenal gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON40671

Source
ToetsingOnline

Brief title
Recovery of the HPA axis during glucocorticoid tapering
CURVE

Condition

- Adrenal gland disorders
- Autoimmune disorders
- Vascular disorders NEC

Synonym
adrenal insufficiency, secondary adrenal insufficiency

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ANCA-associated vasculitis, Cortisol, Hypothalamic-pituitary-adrenal axis Glucocorticoids

Outcome measures

Primary outcome

The main study endpoint is change in peak cortisol levels at acrophase during a glucocorticoid tapering regime.

Secondary outcome

Secondary endpoints include the effect on cortisol ratios or indices of cortisol production, which might prove to be helpful in assessing adrenal function or might be suggestive for impaired recovery or adrenal insufficiency. Furthermore, the effect of the tapering regime on melatonin rhythm, cytokine profile, complaints compatible with secondary glucocorticoid-induced adrenal insufficiency, quality of life, fatigue and sleep quality.

Study description

Background summary

Glucocorticoids are extensively used for a wide-variety of diseases. In many diseases, amongst others rheumatic diseases, high-dose glucocorticoids are administered to control disease activity. These supra-physiological glucocorticoid doses suppress the endogenous cortisol production and disrupt the circadian rhythm of the hypothalamic-pituitary-adrenal (HPA) axis. In order to prevent relapses and to give the adrenal glands time to recover the endogenous cortisol production, tapering regimes are used for glucocorticoid withdrawal. However, no longitudinal studies have investigated the effect of a

tapering regime on the recovery of the circadian rhythm of the HPA axis and the relation with complaints possibly compatible with secondary adrenal insufficiency.

Study objective

The primary aim of this study is to investigate the recovery of the circadian rhythm of the hypothalamic-pituitary-adrenal axis during a glucocorticoid tapering regime. Secondary objectives include the effect of a tapering regime on melatonin rhythm, cytokine profile, complaints compatible with secondary glucocorticoid-induced adrenal insufficiency and quality of life, fatigue and sleep quality.

Study design

This is a longitudinal observational pilot study.

Study burden and risks

Burden: On seven separate days in an 8-month period subjects will collect saliva approximately every one or two hour during a 24-hour period. The 24-hour sampling will take place at prednisolone dosages of 10 mg, 7,5 mg, 5 mg, 2,5 mg and 4 weeks, 3 months and 6 months after discontinuation of the prednisolone. In addition, subjects will collect 24-hour urine during the seven 24-hour time points. Blood samples will be drawn at the following visits to the outpatient clinic at 7 time points. Questionnaires regarding somatic complaints, quality of life, fatigue, anxiety and depression and sleep will be completed at the outpatient clinic at 7 time points. At the last visit a Synacthen test will be performed to test the adrenal function.
The healthy controls will only collect saliva and urine during an 24 hour period. They will not undergo any of the other measurements.
Risk: In this observational study, a glucocorticoid tapering regime according to standard patient care in the University Medical Center Groningen (UMCG) will be used. Saliva and urine collection are safe and not invasive. At 7 time points blood samples will be drawn. Blood sampling will be performed simultaneously with blood sampling for standard patient care at five of the 7 time points. The Synacthen test is the standard diagnostic test to diagnose adrenal insufficiency. The adrenal glands will be stimulated with synthetic ACTH (Synacthen) to study the capacity of the glands to produce a maximum level of cortisol. Side effects are transient and rarely severe.
Group relatedness: In subjects with GPA and MPA the glucocorticoid tapering regime is a uniform protocol, which is used in several hospitals.
Benefit: this study will give insight in the recovery of the HPA axis and whether recovery or impaired recovery might be related to commonly expressed complaints by patients while on a tapering regime. Therefore this study will add important information and might serve as pilot for future studies comparing

different tapering regimes which should ultimately minimize complaints of patients and the risks of secondary glucocorticoid-induced adrenal insufficiency.

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

Patient with newly diagnosed granulomatosis with polyangiitis or microscopic polyangiitis who received standard glucocorticoid induction protocol
Patients with a relapse of granulomatosis with polyangiitis or microscopic polyangiitis who received standard glucocorticoid induction protocol
Provide written informed consent

Exclusion criteria

Applicable for patients and healthy controls
Age < 18 years
Use of > 7,5 mg of glucocorticoids for more than 4 consecutive weeks within 6 months prior to study inclusion.
Premenopausal women (because of effects of estrogens on cortisol binding globulin and because of differences in HPA axis functioning in the luteal or follicular phase)
Postmenopausal women using oral contraceptives or estrogen replacement therapy (since estrogens increase the hepatic production of cortisol binding globulin)
A history of endogenous hypocortisolism or hypercortisolism prior to this study
Work in shifts or have a documented severely disturbed sleep pattern
Not able to perform saliva sampling
Persons who have a significant other medical condition (e.g. hepatic, respiratory, cardiovascular or gastrointestinal) which, in the opinion of the investigator, may interfere with the interpretation of results or efficacy evaluations
Traveled through time zones with more than two hours time difference within the last month prior to this study
Use of exogenous melatonin within the last 6 months prior to this study
A documented depression
Subjects who are in a stressful situation (for example, death of a relative), which in the opinion of the investigator, may interfere with the interpretation of results or efficacy evaluations

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-03-2015

Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	07-08-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-12-2017
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

ID: 29371
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL49307.042.14
OMON	NL-OMON29371