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Time course of hypothalamic-pituitary adrenal alterations in response to critical illness

Submission date 11/11/2014	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 30/12/2014	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 05/11/2018	**Condition category** Other	[_] Individual participant data

Plain English summary of protocol

Background and study aims

When we are stressed, the concentration of a hormone called ACTH in the blood rises. This, in turn, increases the amount of stress-hormone cortisol released from the adrenal gland. However, in intensive care unit (ICU) patients this stress response seems to be different. Our research group recently showed that during critical illness high blood levels of cortisol are, to a large extent, due a decrease in the amount of cortisol broken down in the body, rather than an increase in the amount of the hormone made. These high cortisol levels could in their turn stops the release of ACTH by what is called 'negative feedback inhibition'. It is possible that when circulating ACTH levels remain low for too long, the patients adrenal glands may become affected, resulting in a condition called 'relative adrenal failure'. We want to investigate how circulating cortisol and ACTH levels change over time in ICU patients. We will also look at how the adrenal glands respond to an extra stimulation by ACTH. This will allow us to gain further insights in the recovery of ACTH and cortisol levels in the blood as well as what leads to relative adrenal failure.

Who can participate?

Adult patients that have been in ICU for at least 7 days. Healthy individuals will be recruited to match with the patient group.

What does the study involve?

To investigate the changes in ACTH and cortisol during critical illness, urine samples and blood samples are collected daily from critically ill patients from day 7 until day 28 of their ICU stay. A test that stimulates the production of ACTH (ACTH stimulation test) is performed weekly. In patients staying more than 28 days, an additional blood sample, urine sample and ACTH stimulation test is taken weekly until the patient is discharged from the ICU. On the last day in ICU an additional blood sample is collected. After discharge from ICU to a regular ward, a final blood sample and ACTH stimulation test are taken on day 7 after discharge from the ICU or on the day of discharge from the hospital before day 7.

What are the possible benefits and risks of participating?

There will be no immediate benefits or risks for participants in the study. Taking a small amount of blood on day 7 after discharge from the ICU may cause mild pain, bruises or minimal bleeding.

Where is the study run from?
Five ICUs of the University Hospitals of Leuven (Belgium).

When is the study starting and how long is it expected to run for?
December 2014 to November 2015

Who is funding the study?
Methusalem (long term structural funding by the Flemish Government, Belgium), Research Foundation - Flanders (FWO) (Belgium) to the KU Leuven.

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
S57249

Study information

Scientific Title
On the dynamics of the hypothalamus-pituitary-adrenal axis response to prolonged critical illness: a prospective observational study

Acronym
Dynamic Adrenal Study (DAS)

Study objectives
Recently it was shown that during critical illness reduced cortisol metabolism contributes to hypercortisolism while cortisol production is only mildly elevated, if at all [Boonen et al., NEJM 2013]. Maintaining high circulating cortisol levels could suppress ACTH secretion via negative feedback inhibition. It remains unknown whether/when ACTH secretion recovers in ICU patients and whether/when the continuously suppressed circulating ACTH during prolonged critical illness is causing adrenal insufficiency. Also, the use of a single ACTH stimulation test for the diagnosis of adrenal failure in this condition is highly debated, because it is poorly reproducible in critically ill patients and may simply reflect the degree of negative feedback inhibition exerted by the cortisol that is not broken down. Therefore our primary objective is to characterize the time course of the HPA-axis changes and the response to exogenous ACTH during prolonged critical illness and upon recovery. Our secondary objective is to address the causes /consequences of these changes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee (Institutional Review Board) of the University Hospitals Leuven, 30/10/2014, ref: ML11107

Study design
Observational cohort study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Critical illness

Interventions
To evaluate the evolution of the HPA-axis alterations during critical illness, 24h-urine collection samples and blood samples (4 ml) will be collected daily in critically ill patients from day 7 until day 28 of their ICU stay to determine evolution of ACTH and cortisol plasma concentrations and

urine cortisol metabolites. A short ACTH-stimulation test (injection of 250 µg Synacthen®) will be performed weekly. In patients staying more than 28 days, a minority of the ICU population, an additional blood sample (4 ml), 24 h urine collection and ACTH-stimulation test will be taken weekly until ICU discharge or death. On the last day in ICU an additional blood sample (4 ml) will be collected to quantify plasma ACTH and cortisol concentrations at recovery/death. After discharge from the ICU, a final blood sample and ACTH stimulation test will be taken on day 7 post-ICU or on the day of discharge in patients discharged from the hospital before day 7.

Intervention Type
Other

Primary outcome measure
1. Determination of the evolution of ACTH and cortisol plasma concentrations and urine cortisol metabolites during prolonged critical illness and upon recovery, in comparison with ACTH and cortisol plasma concentrations of healthy volunteers.
2. To characterize the time course of the response to exogenous ACTH during prolonged critical illness and upon recovery, in comparison with response to exogenous ACTH in healthy volunteers.

Secondary outcome measures
Further mechanistic analyses using clinical and laboratory parameters.

Overall study start date
01/12/2014

Completion date
31/07/2017

Eligibility

Key inclusion criteria
For patients:
1. Critically ill patients admitted for ≥7 days to one of the five ICUs from two departments (medical and surgical) in the University Hospitals Leuven
2. Age ≥18 years

For healthy volunteers:
1. Age-, gender- and BMI-matched to the included patients

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
At least 542 patients (not receiving exogenous steroids) staying more than 7 days at the ICU and 20 healthy matched volunteers

Key exclusion criteria
For patients:
1. Predisposing factors of adrenal insufficiency:
1.1. Cerebral disease with intracranial hypertension threatening the neuroendocrine system
1.2. Pituitary disorders including (pan)hypopituitarism
1.3. Known adrenal disease (Cushing's syndrome or Addison's disease)
1.4. Treatment with glucocorticoids, other steroids or anti-steroid chemotherapy within the last 3 months
1.5. Use of etomidate within the last 72 hours
1.6. Other drugs predisposing to adrenal insufficiency: azoles, phenytoin, rifampicin, glitazones, imipramin, phenothiazine, phenobarbital
2. No arterial line in place
3. Ethical restrictions:
3.1. Moribund
3.2. Declined participation

For healthy volunteers:
1. Recent history of treatment with HPA-axis interfering drugs

Date of first enrolment
01/12/2014

Date of final enrolment
31/07/2017

Locations

Countries of recruitment
Belgium

Study participating centre
University Hospitals Leuven (UZ Leuven)
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Sponsor information

Organisation
KU Leuven

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Sponsor type
Research organisation

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ROR
https://ror.org/05f950310

Funder(s)

Funder type
Government

Funder Name
Methusalem (long term structural funding by the Flemish Government, Belgium), Research Foundation - Flanders (FWO) (Belgium)

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/10/2018		Yes	No