# The influence of ACTH on blood coagulation

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The primary objective of this clinical controlled trial is to define the overall effect of adenocorticotropic hormone on coagulation parameters in patients with primary adrenal insufficiency (as diagnosed by their physician by previous short ACTH...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Coagulopathies and bleeding diatheses (excl thrombocytopenic) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON34344

**Source**
ToetsingOnline

**Brief title**
ACTH study

### Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Endocrine and glandular disorders NEC
- Embolism and thrombosis

**Synonym**
blood clothing system

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Slotervaartziekenhuis
**Source(s) of monetary or material Support:** vanuit geld voor onderzoek binnen de afdeling interne geneeskunde Slotervaart ziekenhuis en de afdeling vasculaire geneeskunde

AMC

## Intervention

**Keyword:** ACTH, adenocorticotrope hormone, coagulation, fibrinolysis

## Outcome measures

### Primary outcome

• Coagulation activation markers F1+2 and ETP. If increased, the following will be tested: thrombin-antithrombin complexes (TAT), factor VII:C.

• Endothelial cell activation and platelet activation markers von Willebrand factor antigen (vWf:Ag) and von Willebrand factor activity (vWf:RiCof). If increased, the following will be tested: thrombomodulin, P-selectin.

• Clotting factor VIII activity (fVIII:C).

• Fibrinolysis activation markers: plasmin-antiplasmin complexes (PAP) and D-dimer. If increased, the following will be tested: tissue-type Plasminogen Activator (t-PA), urokinase-type plasminogen activator (u-PA), Plasminogen Activator Inhibitor-1 (PAI-1) activity and antigen.

• Blood coagulation time: PT, aPTT.

### Secondary outcome

not applicable

# Study description

### Background summary

Adrenocorticotropic hormone (ACTH), also known as corticotropin, is a polypeptide tropic hormone secreted by the anterior pituitary gland. It is an important component of the hypothalamic-pituitary-adrenal (HPA) axis and its principal effects are increased production and release of cortisol from the

adrenal cortex (1).

ACTH is most commonly used for diagnosing adrenal insufficiency. The therapeutic use of ACTH is still under investigation. It is used as a treatment for infantile spasms (West syndrome) (2). The use of ACTH for the treatment of shock conditions and of respiratory and cardiocirculatory insufficiencies has been the subject of extended examination. Studies have shown the potential usefulness of ACTH as first-aid treatment in cases of severe blood losses (3-5). Recently, it was discovered that ACTH and melanocyte-stimulating hormones, collectively called melanocortin peptides, together have multiple effects on the host. Activation of melanocortin receptors, found in many different cell types, could be a novel strategy to control inflammation.(6) Whether activation of these receptors could influence the hemostatic system is however not known.

Ever since the early 1950*s, several studies have focused on the relation between ACTH and the coagulation system and the possible therapeutic use of ACTH in surgery. Reports on the effect of ACTH on the haemostatic system, however, are conflicting. In in vivo studies several coagulation abnormalities have been reported after administration of ACTH. Two studies found a temporary thrombocytosis both in normal and in thrombopenic subjects after administration of ACTH (7; 8). Cosgriff et al, found a shortening of the venous clotting time suggesting a state of hypercoagulability (9). Smith et al, on the contrary, found prolongation of the venous clotting time (10). In a study performed by Chatterjea an increased incidence of thromboembolic compications during ACTH and cortisone therapy was found and a higher dosage of anticoagulants was needed to obtain plasma prothrombin activity at the optimum level (11). Mc Graw et al suggested a differential effect of ACTH on blood clotting: in the right dose a hypocoagulable state was observed, with a dramatic improvement in signs and symptoms and the favourable changes in the prothrombin times and heparin levels, whereas a hypercoagulable state was found after administration of massive doses or sudden withdrawal. They would possibly implicate the therapeutic use of ACTH in the acute phase of a phlebothrombosis but also state the potential danger that ACTH may finally induce a prothrombotic state (12).

Chronic endogenous and exogenous hypercortisolism are known to induce a hypercoagulable state (13). In Cushing*s syndrome a higher incidence of venous thromboembolic events was found (14). Therefore, it remains uncertain whether the coagulation abnormalities found in the studies mentioned can be attributed to the direct effect of ACTH or to an increased level of cortisol produced by the adrenal gland following ACTH administration. Hutton et al found a decrease in platelet aggregability after an intramuscular injection of tetracosactrin (1-24 ACTH) with a rise in plasma cortisol concentration. Intravenous injection of hydrocortisone however, had no effect on platelet aggregation (15). Fahey failed to detect any significant alteration of the coagulation time after injection of ACTH in normal human subjects or in patients with hypo-or hyperadrenocortisism (16).

Most published studies have important methodological drawbacks. Lack of a control group, small study size, and (at this moment) obsolete laboratory assays obscure the real in vivo effects of administrated ACTH on the haemostatic system.
Also, none of these studies have shown direct activation of coagulation or inhibition of fibrinolysis despite the individual haemostatic changes observed after administration of ACTH. As such, studies including measurements of endogenous thrombin generation and overall fibrinolytic activity (prothrombin fragment 1+2, thrombin generation test, plasmin-antiplasmin complex) are needed to clarify the suggestion of a hypercoagulable and hypofibrinolytic state after administration of ACTH. Moreover, better differentiation between the separate effects of ACTH and cortisol is needed. Therefore, the aim of this study is to determine the effect of ACTH on the activation of coagulation and inhibition of fibrinolysis by performing short ACTH stimulation tests in patients with primary adrenal insufficiency.

## Study objective

The primary objective of this clinical controlled trial is to define the overall effect of adenocorticotropic hormone on coagulation parameters in patients with primary adrenal insufficiency (as diagnosed by their physician by previous short ACTH stimulation tests showing no rise in cortisol after injection with Synacthen) without the obscuring effects of endogenous corticosteroid excretion.

Secondary objectives
To define the specific effect of ACTH on each of the following coagulation and fibrinolytic parameters:
1) Prothrombin fragment 1+2 (F1+2)
2) Von Willebrand factor antigen (vWfAg)
3) D-dimer
4) Prothrombin time (PT)
5) Activated partial thromboplastin time (aPTT)
6) von Willebrand factor ristocetin cofactor activity
7) factor VIII:C
8) Plasmin-antiplasmin complex (PAP)
9) Thrombin generation test (ETP)

## Study design

Phase 1: pilot study
Phase 2: clinical controlled trial

Study design
Phase 1: We will first carry out a pilot study in which we will perform a short ACTH stimulation test in 10 patients who are planned for this test in their

diagnostic process for the outpatient clinic. We will strive to include 10 patients with a normal rise in cortisol after injection with Synacthen, therefore patients found to have an abnormal rise in cortisol will not be included for the final analysis in this pilot study. Ten healthy volunteers will serve as controls and will be injected with 1 ml saline solution instead of 1 ml (250 µg/ml) tetracosactide (Synacthen). The volunteers will be recruited through advertisements and carefully screened before enrolment. A venflon for intravenous access will be placed once, 30 minutes before first blood withdrawal, and will be kept in place for blood withdrawal and Synacthen administration for the entire duration of this study.
If we indeed find significant differences in coagulation parameters before (t=0), 1 hour (t=1), 3 hours (t=3) and 6 hours after the testing after the injection of Synacthen (t=6), the protocol as described at phase 2 will be put into operation. Any changes in this protocol will be sent to the METC as amendment.

Phase 2: This study is a clinical controlled trial in which patients with known primary adrenal insufficiency (as diagnosed by their physician by previous short ACTH stimulation tests, showing no rise in cortisol after injection with Synacthen) will undergo short ACTH stimulation testing in the early morning. The test will be performed at two times in the study. The first visit the cases will be asked to normally take in there morning dose of hydrocortisone substitution therapy. The second visit, at least 30 days after the first visit, they will be asked not to take their hydrocortisone substitution therapy until after the short ACTH stimulation test has been performed. Blood will be drawn as described at phase 1. This way we can determine the effect of ACTH in patients with hypocortisolism and eucortisolism. The healthy volunteers and patients with no abnormalities found in the short ACTH stimulation test, as described at phase 1, will serve as controls.
If we indeed find a patient with primary adrenal insufficiency (no rise in cortisol after injection of synacthen) at phase 1 of this study, the results of this patient will be included in phase 2. This patient will be asked to come back for a second Synacthen test with the normal hydrocortisone substitution.

**Intervention**

Phase 1: We will first carry out a pilot study in which we will perform one short ACTH stimulation test on 10 patients in light of routine laboratory testing. Ten healthy volunteers will serve as controls and will be injected with saline solution instead of Synacthen. If we indeed find significant differences in coagulation parameters before (t=0) and1 hour (t=1), 3 hours (t=3) and 6 hours after the injection of Synacthen (t=6) compared to the control group, the protocol as described at phase 2 will be put into operation.
Phase 2: The short ACTH stimulation test will be performed two times. The first visit the cases will be asked to normally take in there morning dose of hydrocortisone substitution therapy. The second visit they will be asked to not take their hydrocortisone substitution therapy until after the short ACTH

stimulation test has been performed. The healthy volunteers and patients with no abnormalities found in the short ACTH stimulation test, as described at phase 1, will serve as controls.

**Study burden and risks**

Phase 1: the ACTH test is not being performed for this study specifically, the physician of the outpatient clinic has ordered the test, the only risk related to this study in this phase is placement of a venflon. If this phase does not show an influence we will not have to expose patients with an established adrenal insufficiency to any risk.

Phase 2: As patients with adrenal insufficiency depend on hydrocortisone substitution therapy, delaying the intake of hydrocortisone until after the short ACTH stimulation test is performed, implies a small risk of developing symptoms of cortisol deficiency, and even smaller risk of "adrenal crisis". For this reason every test will be performed under strict supervision of the investigator. In case a patient develops symptoms indicating severe adrenal insufficiency the test will immediately be ceased and an infusion of isotonic sodium chloride solution will be begun to restore volume deficit and correct hypotension. We will also immediately start hydrocortison (Solucortef) 100 mg i.v. bolus followed by 200-500 mg/24h. The patient will be hospitalized until a stable situation has been reached.

# 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

Phase 1: Patients and healthy volunteers
a. Adults >= 18 years old.
b. Informed consent.;Phase 2. Cases
a. Adults >= 18 years old.
b. Informed consent.
c. Primary adrenal insufficiency defined as:
1) Bilateral adrenalectomy
2) Auto-immuun adrenalitis
3) Congenital adrenal hypoplasia/ adrenal dysgenesis

## Exclusion criteria

Phase 1.
a. Use of oral contraceptive agents, corticosteroids, anticoagulants, platelet aggregation inhibitors and NSAIDs.
b. Known or suspected hypersensitivity to Synacthen; poorly controlled asthma; pregnancy and lactation; untreated acute or chronic bacterial, fungal and viral infections; diabetes mellitus type II; Cushing's syndrome; refractory congestive heart failure; active or latent peptic ulcer; acute psychosis; non-specific ulcerative colitis; diverticulitis; recent intestinal anastomosis; renal insufficiency (kreatinin > 200 umol/l); liver failure (ALAT, ASAT, yGT, AF > 3 times normal value); hypertension (systolic pressure above 140); myasthenia gravis or malignancy.;Phase 2.
1) Congenital adrenal hyperplasia (CAH)
2) Secondary adrenal insufficiency
3) Tertiary adrenal insufficiency
4) Primairy adrenal insufficiency induced by:
a. Steroid synthesis inhibitors (e.g., metyrapone, ketoconazole, aminoglutethimide)
b. Adrenolytic agents (o,p'DDD, suramin)
c. Glucocorticoid antagonists (RU 486)
d. Metastatic neoplasia/infiltration
e. Criteria mentioned at phase 1 with the exception of corticosteroid use.

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Placebo |
| Primary purpose: | Basic science |

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 25-02-2011 |
| Enrollment: | 30 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 31-05-2010 |
| Application type: | First submission |
| Review commission: | METC Slotervaartziekenhuis en Reade (Amsterdam) |
| Approved WMO Date: | 22-12-2010 |
| Application type: | Amendment |
| Review commission: | METC Slotervaartziekenhuis en Reade (Amsterdam) |

# 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 |
| --- | --- |
| CCMO | NL32152.048.10 |