The Efficacy of TRH in Intensive Care patients; a dose finding study

Published: 04-08-2016
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To determine the minimal dose of protirelin that is effective and safe to normalize plasma thyroid hormone levels in patients with prolonged critical illness.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON46988

Source
ToetsingOnline

Brief title
The ETHIC Trial; Dose finding pilot study

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Non thyroidal illness syndrome; changes in thyroidhormone metabolism due to non thyroid related illness

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Critical illness, Non thyroidal illness syndrome, Thyrotropin releasing hormone

Outcome measures

Primary outcome

The primary endpoint of the study is the change in T3 concentration after

treatment with protireline.

Secondary outcome

The secondary endpoints of the study are thyroid hormone concentrations (T3,

T4, fT4, rT3 and TSH), metabolic markers including urea, creatinine and the

bone markers CTx and P1NP before, and during 1 and 2 weeks of treatment.

Study description

Background summary

A broad variety of illnesses is known to induce a set of profound changes in thyroid hormone metabolism, collectively known as non-thyroidal illness syndrome (NTIS). Its main characteristics are decreased plasma levels of circulating thyroid hormone (TH) in the absence of an increase in thyroid stimulating hormone (TSH), indicating a major change in feedback regulation of the hypothalamic-pituitary-thyroid axis (HPT axis). Some investigators have hypothesized that the persistent down-regulation of the HPT axis has detrimental effects on clinical outcome in patients with prolonged critical illness, but this has not been adequately tested to date. There is a clear need for randomized clinical trials addressing this issue (for review see Fliers et al, 2015). We intend to perform a randomised controlled study in patients with prolonged critical illness using protirelin, the pharmaceutical form of thyrotropin releasing hormone (TRH), to restore plasma TH to within the reference range. Protirelin is registered for use as a diagnostic test for thyroid and pituitary function. As a first step, we will perform a dose finding study with protirelin in critically ill patients aimed at restoring plasma TH concentrations.

Study objective

To determine the minimal dose of protirelin that is effective and safe to normalize plasma thyroid hormone levels in patients with prolonged critical illness.

Study design

Phase II dose finding study, open label with a step-up design.

Intervention

Subjects will receive protirelin (TRH) intravenously until the end of their stay in the intensive care but with a minimum treatment duration of 5 days and a maximum treatment duration of 2 weeks. Up to three doses will be tested in a step-up design (1, 1.5 & 2 µg/kg/h) in 8 patients. 8 patients will be included as controls without an intervention.

Study burden and risks

The burdens associated with this study are frequent blood sampling and intravenous infusion of protirelin. Protirelin will be administered intravenously by continuous infusion over an in situ venous catheter inserted for routine clinical purposes. Blood (18ml) will be drawn daily from an in situ arterial catheter inserted for clinical purposes.
Protirelin is a registered drug with no known severe side effects. Previous studies have been performed using protirelin in similar doses in critically ill patients (see references 8-11). Furthermore the effects of TRH administration on serum TH levels are self-limiting. The risk of participation in this study is therefore regarded as minimal and acceptable, even in this vulnerable patient population.

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

Aged *18
Admitted to the ICU for at least 1 week prior to inclusion
Expected duration of further stay *5 days
Systemic treatment with morphine or other opioids

Exclusion criteria

* Known pre-existing thyroid disease
* Treatment with drugs aimed at restoring biochemical euthyroidsm (methimazole, propylthiouracil, triiodothyronine and levothyroxine) and amiodarone.
* Treatment with heparine at a therapeutic (thrombolytic) dose (*10.000 IE/24h)
* Treatment with somatostatin or dopaminergic drugs
* Current glucocorticoid use or glucocorticoid use within *48 hours prior to study start
* Renal failure requiring dialysis or hemofiltration
* Pregnancy

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	thyrotropin releasing hormone / protirelin
Generic name:	protirelin

Ethics review

Approved WMO Date:	04-08-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2018
Application type:	Amendment
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	EUCTR2016-001006-41-NL
CCMO	NL57121.018.16