Hepcidin kinetics in hemodialysis patients.

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Observational invasive

Summary

ID

NL-OMON34512

Source
ToetsingOnline

Brief title
Hepcidin and hemodialysis.

Condition

- Anaemias nonhaemolytic and marrow depression
- Renal disorders (excl nephropathies)
- Renal and urinary tract therapeutic procedures

Synonym
haemodialysis, treatment with artificial kidney

Research involving
Human

Sponsors and support

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

Intervention

Keyword: erythropoietin, hemodialysis, hepcidin, iron

Outcome measures

Primary outcome

Serum and dialysate hepcidin-25 and its two smaller isoforms hepcidin-22 and

20.

Secondary outcome

not applicable

Study description

Background summary

Anemia is common in patients with renal insufficiency and erythropoietin (EPO)-deficiency is by far the major cause. Since 1998 patients with CKD are widely treated with erythropoietin agents (ESA). About 10% of patients are hypo- or unresponsive to ESA. This is problematic: several recent studies indicate that ESA-resistance is associated with increased cardiovascular morbidity and mortality. The underlying mechanism remains to be clarified, but the adverse cardiovascular effects may be due to some off-target effect of ESA. Iron deficiency contributes to ESA-resistance and the majority of HD patients receive IV iron aiming to maintain ferritin levels between 200-600 ng/ml. However, traditional markers of iron status are inaccurate in HD and iron is a potential toxin. Hepcidin is a key regulator of iron metabolism. Recently hepcidin over-expression in mice was associated with resistance to ESA. Moreover, antibody treatment neutralized hepcidin in vivo and facilitated anemia treatment in these mice. Hepcidin could thus become an important tool to predict ESA responsiveness, and to guide treatment with ESA and IV iron. Hepcidin could even become a potential target of treatment in patients with CKD.

Study objective

Serum hepcidin levels are elevated in hemodialysis patients and may contribute to functional iron impairment and thus to ESA-resistance. Kinetics of hepcidin in hemodialysis patients has not been studied in detail. This study is designed to provide an answer to the following questions:

1. Do the type of dialysis membrane, the dialysis mode, and/or the dialysis duration influence hepcidin clearance?
2. Does administration of IV EPO/iron influence serum hepcidin levels in patients requiring hemodialysis?
3. Are changes in hepcidin levels after dialyses and/or therapeutic interventions quickly counter-regulated in dialysis patients?

Results will be used for the design and execution of large multicenter pan-European study on hepcidin as a tool to predict ESA-responsiveness, to guide ESA and iron treatment in CKD.

Study design

1. Do the type of dialysis membrane (e.g. low vs high-flux, polysulphon vs polyamide vs polyacrylonitrile), the dialysis mode (hemodiafiltration/hemodialysis), and the dialysis duration influence hepcidin clearance?
In order to evaluate the in vivo effect of the dialysis technique on serum hepcidin kinetics, serum hepcidin levels will be measured before and 30 minutes after the end of the hemodialysis session. In addition samples will be drawn from the arterial (blood flowing to the dialyzer) and the venous (blood flowing to the patient) line to assess the arterio-venous differences at the beginning and at the end of the dialysis session. Dialysate samples will be collected at the same time points in order to calculate clearance.

Various conditions will be compared:
• Several different dialysis membranes (low-flux vs high-flux, polyamide vs polysulphonvs polyacrylonitrile).
• Hemodialysis versus hemofiltration

8-10 patients will be studied during each experiment in a crossover design. Patients will be studied using at least 2 and at most 5 different dialysis techniques. During each session 50 ml blood will be collected. Thus, maximal 250 ml blood will be drawn in total. Patients will not receive IV iron or EPO during experimental dialysis sessions.

2. Does administration of IV EPO/iron influence serum hepcidin levels in patients requiring hemodialysis?
To evaluate the short-term effects of IV iron and EPO serum hepcidin levels will be measured before administration of IV iron or IV EPO and 1,2,4 and 8 hours afterwards. Samples will be collected from the arterial line. Studies will be conducted in patients who are regularly treated with IV iron/EPO (n=8-10 in each group, total 16-20) before and after withholding IV iron and EPO for at least 2 weeks. Total number of samples amounts to 5 per session (50 ml blood). A patient will be studied during maximal 4 different conditions.

3. Are changes in hepcidin levels after dialyses and therapeutic interventions

quickly counter regulated in dialysis patients?
After interpretation of data obtained by the above experiments, regulation of hepcidin will be studied more extensively in those patients/conditions where serum hepcidin levels were most notably altered (see point 1 and 2). In these patients, similar experiments will be performed resulting in considerably decreased hepcidin levels. Serum hepcidin levels will be then monitored at regular intervals (1,2,4, 8 and 24 hours) after the nadir of hepcidin. In total 50-80 ml blood will be drawn per patient.

We hypothesize that the kinetics of serum hepcidin may be partly dependent on iron status and inflammatory responses. Therefore, in all studies blood samples will be drawn for assessment of baseline ferritin, sTfR, iron, transferrin, % hypochromic erythrocytes, hs-CRP, IL-6, Hb, Ht, MCV, MCH, ret Hb , and reticulocytes.

Hepcidin-25 and its two smaller isoforms hepcidin-22 and 20 will be quantitated by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), preceded by hepcidin enrichment by weak cation exchange (Peters, NDT 2009; Swinkels, PLoS One 2008).

Studies will be performed in a time period of 6-9 months. Theoretically, patients can participate in experiments described under 1,2, and 3.The total volume of blood may be a burden to patients. Therefore, we will arrange the experiments in such a manner that the total amount of blood will be limited to 400 ml during 9 months.

Study burden and risks

Nature and extent of the burden and risks are considered to be minimal.

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

Adult hemodialysis patients (>18 yrs)
hemodialysis for at least 4 months
no IV iron or EPO during experimental dialysis sessions

Exclusion criteria

malignancies/ overt infection/ hepatic failure, gastro-intestinal bleeding and blood transfusion during the preceding 4 months
no informed consent

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Generic name:	Different dialysis modes
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	31-08-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL32498.091.10