DexaDagen-2 study

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During treatment with dexamethasone, the deprived mineralocorticoid receptor may cause serious cerebral side effects. Hence, it is feasible that these side effects on mood, behaviour and cognition could be prevented, by an intervention with a...

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22781

Source
Nationaal Trial Register

Health condition

Acute lymphoblastic leukemia, behavior, sleep, mood, quality of life, frailty

Sponsors and support

Primary sponsor: Princes Maxima Centre for pediatric oncology
Source(s) of monetary or material Support: Kinderen Kankervrij (KiKa)

Intervention

Outcome measures

Primary outcome

Neurobehavioral problems after 5 days of dexamethasone treatment with or without hydrocortisone addition. These neurobehavioral problems will be measured with the parent-reported SDQ.

Secondary outcome

- Dexamethasone related sleeping difficulties after 5 days of dexamethasone treatment with or without hydrocortisone, measured by the Sleep Disturbance Scale for Children (SDSC) and actigraphy.
- Quality of life after 5 days of dexamethasone treatment with or without hydrocortisone addition, measured with the Pediatric Quality of Life questionnaire (PedsQL).
- The prevalence of frailty and the influence of 5 days of dexamethasone on the different frailty parameters, measured through actigraphy, bio-impedance, ultrasonography, Timed 'Up and Go' test, activity questionnaire and handgrip strength.

Furthermore we will study possible factors influencing the inter-patient variability in developing neurobehavioral side effects:
- Dexamethasone kinetics (i.e. trough and peak levels) and the effect on the development of dexamethasone induced clinically relevant neurobehavioral and sleeping problems.
- Carrier status of candidate single nucleotide polymorphisms (SNPs) and the influence on the development of dexamethasone induced clinically relevant neurobehavioral problems.
- Psychosocial and environmental factors (measured through several questionnaires) that potentially determine the development of dexamethasone induced clinically relevant neurobehavioral problems. - The influence of hydrocortisone addition to dexamethasone treatment on the different frailty parameters.

Study description

Background summary

Objectives:
The primary objective is to validate the finding that addition of physiological doses of hydrocortisone reduces dexamethasone induced clinically relevant neurobehavioral problems.
The secondary objectives are to study frailty in children with ALL, and to investigate whether hydrocortisone addition improves dexamethasone induced sleeping problems, frailty and quality of life. Furthermore we want to determine the role of pharmacokinetics, genetic variation and psychosocial and environmental factors as prognostic factors of dexamethasone-induced neurobehavioral problems.

Study design:
A prospective double blind placebo-controlled randomized cross-over design

Procedure:
Patients will be first enrolled in the Identification study. Patients with clinically relevant dexamethasone induced neurobehavioral side effects will be identified using the Strengths and Difficulties Questionnaire (SDQ). Possible factors influencing the inter-patient variability in developing neurobehavioral side effects will be studied in all patients, as well as the prevalence of frailty. Patients with clinically relevant neurobehavioral side effects will be included in the Intervention part of the study, a randomized controlled trial (RCT).

Study population:
50 patients aged 3-18 years, treated according to the medium risk ALL treatment schedule, with clinically relevant neurobehavioral side effects will be included in the RCT.
As 40% of ALL patients experience the side effects and considering the probability of a 10% dropout rate, a 35% refusal rate and exclusion of 15% based on our exclusion criteria, a total of approximately 360 ALL patients need to be screened. Of these, 275 eligible medium risk patients need to be approached and 150 patients will be included the Identification study.

Intervention:
The intervention consists of 4 identical dexamethasone courses (duration 5 days), during which patients will receive addition of either hydrocortisone (2 consecutive courses) or placebo (2 consecutive courses). Patients will be randomized and cross over will take place after 2 courses.

Main study parameters/endpoints:
• The primary outcome parameter of the Intervention study (RCT) is
o Neurobehavioral problems after 5 days of dexamethasone treatment with or without hydrocortisone addition. These neurobehavioral problems will be measured with the parent-reported SDQ.
• The secondary outcome parameters of the Intervention study (RCT) are
o Dexamethasone related sleeping difficulties after 5 days of dexamethasone treatment with or without hydrocortisone, measured by the Sleep Disturbance Scale for Children (SDSC) and actigraphy.
o Quality of life after 5 days of dexamethasone treatment with or without hydrocortisone addition, measured with the Pediatric Quality of Life questionnaire (PedsQL).
o Frailty and muscle wasting after 5 days of dexamethasone treatment with or without hydrocortisone addition, measured through actigraphy, bio-impedance, ultrasonography, Timed ‘Up and Go’ test, activity questionnaire and handgrip strength.
• Other study parameters, investigated in the Identification part of the study, include:
o Dexamethasone kinetics (i.e. trough and peak levels) and the effect on the development of dexamethasone induced clinically relevant neurobehavioral and sleeping problems.
o Carrier status of candidate single nucleotide polymorphisms (SNPs) and the influence on the development of dexamethasone induced clinically relevant neurobehavioral problems.
o Psychosocial and environmental factors (measured through several questionnaires) that potentially determine the development of dexamethasone induced clinically relevant neurobehavioral problems.
o The prevalence of frailty and muscle wasting, and the effect of 5 days of dexamethasone treatment.

Study objective

During treatment with dexamethasone, the deprived mineralocorticoid receptor may cause serious cerebral side effects. Hence, it is feasible that these side effects on mood, behaviour and cognition could be prevented, by an intervention with a natural occurring hormone that stimulates the mineralocorticoid receptor in the brain in a physiological way. This can be done by adding physiological dosages of cortisol (hydrocortisone) during dexamethasone treatment. Our recently reported randomized controlled trial, the DexaDagen-1 study

(NTR3280), showed that clinically relevant neurobehavioral problems decrease by hydrocortisone addition during dexamethasone treatment. Validation of these results is required in a selected larger sample. The safety of hydrocortisone addition to dexamethasone treatment has been ensured before in a preclinical study, and showed no interference of hydrocortisone with the anti-leukemic efficacy of dexamethasone.

Study design

Patients will start at T1 when they are in maintenance phase, after cessation of asparaginase. Neurobehavioral assessment will take place for approximately 150 patients on T1 and T2. On these timepoints the possible factors influencing inter-patient variability in developing neurobehavioral side effects will be studied as well. In addition, the different frailty parameters will be measured at T1 and T2.
50 patients with clinically relevant neurobehavioral side effects will be included in the intervention study (RCT). This consists of 4 identical dexamethasone courses (duration 5 days; T3-4; T5-6; T7-8; T9-10), during which patients will receive addition of either hydrocortisone (2 consecutive courses) or placebo (2 consecutive courses). Neurobehavioral assessment will take place on every timepoint (T3-T11). Furthermore, sleep, quality of life and frailty parameters will be measured during the first hydrocortisone and placebo course (T3-4 and T7-8). Frailty will be measured on T3, T7 and T11.

Intervention

The intervention consists of 4 identical dexamethasone courses (duration 5 days), during which patients will receive addition of either hydrocortisone (2 consecutive courses) or placebo (2 consecutive courses). Patients will be randomized and cross over will take place after 2 courses.

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Eligibility criteria

Inclusion criteria

- Written informed consent
- Age 3-18
- Confirmed diagnosis of acute lymphoblastic leukemia (ALL)
- Inclusion in DCOG ALL medium risk group protocol
- Able to comply with scheduled follow-up

Exclusion criteria

- Patient or parent refusal
- Anticipated compliance problems
- Underlying conditions which affect the absorption of oral medication
- Pregnant or lactating patients
- Current uncontrolled infection or any other complications which may interfere with dexamethasone treatment
- Language barrier
- Pre-existing mental retardation

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2018
Enrollment:	105

Type: Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion
Date: 05-09-2017

Application type: First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50327
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL6507
NTR-old	NTR6695
CCMO	NL62388.078.17
OMON	NL-OMON50327

Study results