The 'how to survive my dex days' 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...

Ethische beoordeling	Niet van toepassing
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23013

Bron
Nationaal Trial Register

Aandoening

- dexamethasone induced cerebral side-effects on mood, behaviour, and cognition
- secondary: other side-effects of dexamethasone; e.g. side-effects like diabetes mellitus, insulin resistance, visceral fat gain, hypertension and hypercholesterolemia

Dutch: neuropsychologische bijwerkingen, stemming, gedrag, cognitie

Ondersteuning

Primaire sponsor: Erasmus Medical Center
Overige ondersteuning: KIKA

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Primary outcome parameter is the parent-reported strength and difficulty questionnaire in Dutch (SDQ-Dut) 20 after 5 days of dexamethasone treatment with or without cortisol. In the general population mean SDQ score is 7,0 (1 SD= 6,0)20 . We expect the mean SDQ-Dut

score of the children after 5 days of dexamethasone treatment to be around 15 in the control group.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale:

The use of dexamethasone (a synthetic corticosteroid) is an essential component for effective treatment of childhood acute lymphoblastic leukemia (ALL). However, it has been reported that in 5-75% of children, treatment with dexamethasone, is accompanied by serious side-effects on mood, cognition and behaviour leading to major effects on wellbeing of children and their parents. In addition, these side-effects often induce therapy adjustments with the risk of decreased effect and subsequent outcome. The exact pathophysiology of the dexamethasone-induced cerebral side-effects is unknown but has been presumed to be mediated by its effect on the glucocorticoid receptor. Dexamethasone suppresses endogenous production of cortisol. Recent findings show that lack of endogenous cortisol can lead to such side-effects by lack of stimulation of the mineralocorticoid receptor (MR) in the brain. Cortisol dependent mineralocorticoid receptor effects in the brain have been shown to be involved in emotion, memory and sleep. These recent findings led to our novel hypothesis: 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 during dexamethasone treatment. To ensure the safety of this study, we performed a preclinical study, in which we found that adding cortisol to both in vitro cultured leukemic cell lines and ex vivo cultured primary patients¡¦ cells, did not influence the anti-leukemic effect of dexamethasone. Previously, we and others have shown that in vitro dexamethasone sensitivity is strongly associated with clinical steroid response and with clinical outcome.

Objective:

The primary aim of the study is to reduce dexamethasone induced cerebral side-effects on mood, behaviour, and cognition by adding physiological doses of cortisol to standard treatment.

The secondary aim of the study is to analyse the effect of the intervention on other side-effects of dexamethasone; e.g. side-effects like diabetes mellitus, insulin resistance, visceral fat gain, hypertension and hypercholesterolemia.

The third aim of the study is to determine the positive predictive value positive predictive value of the salivary very low dose dexamethasone suppression test with cortisol as a novel in vivo diagnostic test, on dexamethasone side-effects.

Study design:

A prospective double blind placebo-controlled randomized cross-over design.

Study population:

50 patients, aged 3-16 years, treated according to medium risk ALL treatment schedule will be included after informed consent.

Intervention:

During 2 identical periods of 5 days of dexamethasone treatment, in addition, patients will receive either a physiological dose of cortisol (intervention) or placebo.

Main study parameters/endpoints:

1. Questionaires: The parent-reported strength and difficulty questionnaire in Dutch (SDQ-Dut) 20 after 5 days of dexamethasone treatment with or without cortisol;

2. Bloodtest results: Cortisol, lipid spectrum etc;

3. Measurement of blood pressure, BMI, weight;

4. Complaints diary;

5. Food dairy;

6. Neuropsychological test;

7. Physical activity.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Extent and burden is low.

The risk-benefit analysis for the study shows a favorable risk profile. The investigational medicinal product (IMP) that is studied is hydrocortisone, given in a physiological dose, NOT in a pharmacological dose. No side effects are expected in this dose. In addition, we performed pre-clinical in vitro and ex vivo studies to prove that adding cortisol to treatment will not have any negative effects on the efficacy of cytotoxic effect on leukemia cells.

Participants will fill in 4 questionairres on mood, behavior and daily activity, 1 dietary diary (24 hour) at home. They will have 4 neuropsychological tests on cognition, memory and attention during hospital visits (total extra time: 2 hours/visit). In addition they are asked to wear a accelerometer (3x3 cm on their belt) for 2x 5 days (intervention and placebo period) to measure physical activity. Before start of the intervention they will perform once a salivary diurnal cortisol rhythm and a diagnostic salivary very low dose (0,25 mg) dexamethasone suppression test at home, which involves taking 4 salivary samples one day, ingestion of 0,25 mg dexamethasone (weight adjusted) in the evening and one salivary sample the next day. Blood sampling will be done 4 times 2 ml, using the existing vascular access ports, during regular hospital visits, when routine blood tests are already planned.

The intervention drug is widely used and we have ample experience with this drug. The intervention drug is a hydrocortisone, given in a physiological dose, NOT in a pharmacological dose. No side effects are expected in this dose. In addition we performed pre-clinical in vitro and ex vivo studies to prove that adding cortisol to treatment will not have any negative effects on leukemia treatment. As the administered dose of cortisol in the intervention arm of the study is a physiological dose, we do not expect major risks, and hence we will not install a data and safety monitoring board (DSMB) for this study.

Doel van het onderzoek

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 during dexamethasone treatment. To ensure the safety of this study, we performed a preclinical study, in which we found that adding cortisol to both in vitro cultured leukemic cell lines and ex vivo cultured primary patients¡¦ cells, did not influence the anti-leukemic effect of dexamethasone. Previously, we and others have shown that in vitro dexamethasone sensitivity is strongly associated with clinical steroid response and with clinical outcome.

Onderzoeksopzet

For individual profiles of corticosteroid sensitivity the following data will be obtained: salivary diurnal cortisol rhythm (area under the curve), salivary very low dose (0,25 mg) dexamethasone suppression test one week before start of the first dexamethasone course. Neurocognitive tests, questionnaires, blood samples will be done before start and at the end

of the two five-day courses. Patients receive the IMP or the placebo during 2 periods of a 5 day dexamethasone treatment. During each course patients will report in a dietary diary and will wear an accelerometer to measure physical activity.

Onderzoeksproduct en/of interventie

During 2 identical periods of 5 days of dexamethasone treatment, in addition, patients will receive either a physiological dose of cortisol (intervention) or placebo.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Written informed consent;

2. Age 3-16;

3. Histologically or cytologically confirmed acute lymphoblastic leukemia;

4. Inclusion in DCOG ALL10 or ALL11 protocol or ALL R3 protocol;

5. Able to comply with scheduled follow-up.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Patient or parent refusal;

2. Anticipated compliance problems;

3. Underlying conditions which affect the absorption of oral medication;

4. Pregnant or lactating patients;

5. Current uncontrolled infection or any other complication which may interfere with dexamethasone treatment;

6. Language barrier;

7. Preexisting mental retardation syndrome.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-05-2012
Aantal proefpersonen:	50
Type:	Werkelijke startdatum

Ethische beoordeling

Niet van toepassing
Soort: Niet van toepassing

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3129
NTR-old	NTR3280
Ander register	CCMO : 37826
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A