Optimizing timing of glucocorticoid treatment in children with congenital adrenal hyperplasia

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To study the effects of 2 standard treatment timing strategies for glucocorticoid dosage on androgen concentration in CAH children: a. highest dosage in the morning, b. highest dosage in the evening.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Adrenal gland disorders
Study type	Interventional

Summary

ID

NL-OMON48168

Source
ToetsingOnline

Brief title
The Optimed study

Condition

- Adrenal gland disorders

Synonym
CAH, congenital adrenal hyperplasia

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Innovatiefonds

Intervention

Keyword: congenital adrenal hyperplasia, timing, treatment

Outcome measures

Primary outcome

Concentrations of salivary 17OHP and A after 3 weeks of treatment with the 2

different timing strategies.

Secondary outcome

12 hours blood pressure and activity and sleeping patterns during the 2

treatment strategies.

Study description

Background summary

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a disorder of adrenal steroid synthesis caused by a deficiency of one of the enzymes involved in the adrenal steroid synthesis leading to cortisol deficiency (1,2). The compensatory increase in ACTH secretion by the pituitary gland results in stimulation of the adrenal cortex and consequently increased androgen production within the not affected zona reticularis. Females with CAH are born with ambiguous genitalia due to the virilising effect of increased androgens already in utero. In the past, CAH was a life-threatening disease with high morbidity and mortality. Since the introduction of glucocorticoids about 70 years ago, however, mortality and morbidity have been significantly decreased (3-6). Current treatment consists of lifelong replacement of synthetic glucocorticoids. In children usually hydrocortisone is used in a thrice-daily schedule. Treatment guidelines are described in the Dutch CAH guidelines form the Dutch Society of pediatrics (https://www.nvk.nl/Kwaliteit/Werkboeken/Adrenogenitaal-syndroom-AGS). By treatment with glucocorticoids also suppression of the elevated adrenal androgen production can be achieved due to restoring the negative feedback on the pituitary gland. Despite improvement in care and follow-up, many children do not reach final height within their target range and long-term complications (e.g. obesity, hypertension, infertility) are often reported. (1). In most

patients, supra-physiological dosages of hydrocortisone are necessary to decrease androgen production to the normal range in order to prevent side effects such as early pubertal signs, reduced final height, menstrual disturbances and acne but with the risk of complications due to the high glucocorticoid dosages such as also decreased final height, obesity, and cardiovascular complications. Especially the early morning rise of adrenal androgens (around 3.00 am) contributes to cumulative androgen exposure in time and is difficult to suppress. Therefore, balancing of the hydrocortisone dosage is very important. Treatment can be monitored by measuring of 17-hydroxyprogesterone (17OHP) that accumulates before the enzymatic block and the main adrenal androgen androstenedione (A). In the Radboudumc we introduced a non-invasive measurement of this steroids in saliva already more than 20 years ago. Patients usually collect saliva samples three times a day before taking the medication every 3 months before visiting the outpatient clinic. There is still no evidence about the best timing of medication use (4,9). Some centers treat patients with the highest dosage of glucocorticoids in the morning (2/4 * * - * scheme) because this pattern will most likely simulate normal diurnal rhythm of the adrenal gland, whereas other centre use the highest dosage at night around bedtime of the parents (* - * -2/4 scheme) to suppress the early morning increase of androgens more effectively, but with probably negative effects on nocturnal blood pressure and sleeping patterns.

Study objective

To study the effects of 2 standard treatment timing strategies for glucocorticoid dosage on androgen concentration in CAH children: a. highest dosage in the morning, b. highest dosage in the evening.

Study design

6-week cross-over, non randomized strategical multicentre low-interventional trial (category A) A double blind randomized trial is not necessary as the primary and secondary outcome parameters are not influenced by placebo effects https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
After the informed consent procedure, each patient will receive the same total daily medication dosage from their own initial pre-study treatment, starting with either the highest dosage of hydrocortisone in the morning (dosage A: distribution daily dosage 2/4 * 1/4 * *) or in the evening (dosage B: distribution daily dosage 1/4 * 1/4 * 2/4). The first dosage scheme (dosage A or B) will be their own usual medication scheme. Immediately after the first period, the next period of 3 weeks will start. On days 20 and 21 of each 3-week study period, saliva will be collected before taking the medication and one additional measurement at 5 am (a total of 4 samples per day). The patient will collect saliva at home and send the samples to our laboratory by mail. In saliva steroid hormone levels of 17OHP and A will be measured. In the third

week of each treatment cycle, a 12-hour blood pressure profile measurement (19.00 * 7.00h) will be performed. Daily activities will be documented daily by the parents by asking the parents/children to give a daily score (0 * 10) to measure daily activity and sleeping pattern.

Intervention

After the informed consent procedure, each patient will receive the same total daily medication dosage from their own initial pre-study treatment, starting with either the highest dosage of hydrocortisone in the morning (dosage A: distribution daily dosage 2/4 * 1/4 * *) or in the evening (dosage B: distribution daily dosage 1/4 * 1/4 * 2/4). The first dosage scheme (dosage A or B) will be their own usual medication scheme. Immediately after the first period, the next period of 3 weeks will start. On days 20 and 21 of each 3-week study period, saliva will be collected before taking the medication and one additional measurement at 5 am (a total of 4 samples per day). The patient will collect saliva at home and send the samples to our laboratory by mail. In saliva steroid hormone levels of 17OHP and A will be measured. In the third week of each treatment cycle, a 12-hour blood pressure profile measurement (19.00 * 7.00h) will be performed. Daily activities will be documented daily by the parents by asking the parents/children to give a daily score (0 * 10) to measure daily activity and sleeping pattern.

Study burden and risks

We consider the current study a low intervention clinical trial, as per the definition of the EU clinical trial regulation 536/2014. The patient will receive care as usual with hydrocortisone but in two different time patterns. The total daily dosage will be the same in both parts of the study and equal to the pre-study dosage. We do not expect any serious complaints with different dosage patterns. Both treatment strategies are common care in expert centers. The patients are asked to collect 4 saliva samples before taking their medication on 4 different days. For our CAH patients, collecting saliva samples is a standard procedure, which is painless and without complications. The saliva samples will be sent to the laboratory by regular mail. The 12-hour blood pressure profile measurement will be done twice using standard equipment. Parents and children are asked to fill in a digital diary each day during the entire study period. Invasive interventions are not necessary. During the study the patients and their parents will be coached and supported by our research nurse by phone. The team is 24/7 available for questions. The most important international guidelines for CAH (Endocrine Society Guidelines from 2010) pointed out the lack of evidence in the field described above. Our project will lead to better evidence-based guidelines with uniform recommendations within the Netherlands and elsewhere. Effective dosing may lead to lower cumulative elevated androgens more efficiently especially in the night and probably also in lowering of the total hydrocortisone dosage in time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

* Children with congenital adrenal hyperplasia due to 21 hydroxylase deficientie
* Age between 4 and 18 years
* Able to collect saliva

Exclusion criteria

* Other forms of CAH
* Not able to collect saliva
* Chronical medication use other than related to CAH

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-06-2019
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hydrocortisone
Generic name:	Hydrocortisone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-04-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-05-2019
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
EudraCT	EUCTRN168556.091.18-NL
CCMO	NL68556.091.19