A prospective trial with ketoconazole and octreotide combination therapy for treatment of Cushing*s disease.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON36055

Source
ToetsingOnline

Brief title
Ketoconazole/octreotide therapy for Cushing's disease.

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Cushing's disease; pituitary ACTH hypersecretion

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cushing's disease, Medical therapy, Somatostatin receptors

Outcome measures

Primary outcome

Urinary free cortisol

Midnight salivary cortisol

Secondary outcome

Cortisol diurnal rhythm measured in saliva and serum

Quality of life

Parameters of coagulation and fibrinolysis

Bone density and serummarkers for bone turnover

Study description

Background summary

Cushing's disease is caused by an ACTH-producing pituitary adenoma. The primary choice of treatment is surgery, but the long-term remission rate is only 50-70%. Therefore, research is performed to develop alternative treatment modalities. Pituitary irradiation is one of them, but it can take up to a few years for radiotherapy to become effective. Moreover, there is a considerable risk of inducing hypopituitarism. Until now, the role of medical therapy for Cushing's disease is limited. Before surgery, patients are usually pre-treated with ketoconazole. Ketoconazole is an antimycotic agent that, in relatively high dosages, inhibits adrenocortical cortisol production. However, these high dosages are often accompanied by side effects (gastrointestinal, hepatotoxicity), which limits the long-term use of ketoconazole. Corticotroph pituitary adenomas predominantly express the somatostatin receptor subtype (sst) 5 and the dopamine 2 receptor (DA2). Previous studies showed that cabergoline, a DA2 agonist, and pasireotide, a somatostatin analog with high affinity for the sst1, 2, 3 and 5, can be effective with respect to normalizing cortisol levels in patients with Cushing's disease. However, pasireotide can induce hyperglycemia en appears to be able to render patients groth hormone deficient. Cabergoline normalizes cortisol levels in approximately 40% of the

patients that have persistent disease after transsphenoidal surgery.
Octreotide, a somatostatin analog with high affinity for the sst2, is hardly effective in Cushing's disease. This can be explained by the observation that the sst2 is only expressed to a minor extent by corticotroph adenoma cells. In vitro studies with AtT20 cells (a murine cell line that serves as a model for Cushing's disease) showed that the mRNA expression of the sst2 is suppressed by exposure to high concentrations of glucocorticoids. The hypothesis, therefore, is that cortisol-lowering therapy with ketoconazole can induce an up-regulation of the sst2 expression on the adenoma cells. Thereby, the effectivity of octreotide with respect to controlling the ACTH production by the adenoma would increase. Preliminary results from in vitro studies indeed showed that adenomas from patients with normalized preoperative cortiolexcretion had significantly higher sst2 mRNA expression than adenomas from patients with elevated preoperative cortisolexcretion.
Therefore, patients will start with the standard therapy ketoconazole in this study, followed by treatment with octreotide, after which it will be investigated whether octreotide can induce long-term control of hypercortisolism after discontinuing ketoconazole. Regarding the side effects of ketoconazole, this would mean a big improvement in the medical treatment of Cushing's disease. However, if ketoconazole appears unable to normalize the cortisol levels, co-administration of octreotide will not prove to be effective since high levels of cortisol downregulate the sst2 expression of the pituitary adenoma. In that case, ketoconazole will be combined with cabergoline. A preliminary study showed that combination therapy with ketoconazole and cabergoline allows lower dosages of ketoconazole, which decreases the risk of adverse effects.

Study objective

The primary endopoint is to determine whether ketoconazole/octreotide combination therapy, followed by octreotide monotherapy, is an effective treatment for Cushing's disease.
Secundary endpoints address the effects of this therapy on bone metabolism, quality of life and coagulation and fibrinolysis.
Moreover, in patients that do not normalize under ketoconazole monotherapy, we wish to examine the effectiveness of ketoconazole/cabergoline combination therapy.

Study design

Not-randomized, unblinded, prospective intervention study.

Intervention

Ketoconazole treatment (4 times daily 200 mg, maximum 4 times 300 mg during 1 to maximally 5 months)

Octreotide treatment (1 injection every 4 weeks: 20 - 30 mg during 6 to maximally 8 months)
Cabergoline treatment (1 tot 2 mg every other day during maximally 6 months)

Study burden and risks

Routine physical examination and laboratory examination will be performed at baseline and after 3, 6 and 9 months (end of the study period). At baseline and after 9 months, patients will complete quality of life questionnaires.
Patients will visit the outpatient clinic monthly. 24-hour urine and salivary cortisol will be collected at that moment.
In addition, patients will be treated during 9 months, 6 months longer than the usual period preceding surgery. During these 9 months, patients will be treated with ketoconazole (3-5 months, oral administration, maximally 1200 mg daily), octreotide (6-8 months, subcutaneous injection once every 4 weeks) and cabergoline (6 months, oral administration, 1-2 mg every other day). All three drugs have relatively mild adverse effects. Ketoconazole can cause impaired liver function. As indicated in the protocol, the dosage will be lowered in such cases and, if necessary, the drug will be discontinued.

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

Biochemically confirmed ACTH dependent Cushing's syndrome originating from a pituitary adenoma (either de novo, recurrent or residual)

Exclusion criteria

Impaired liver function
Renal insufficiency
Symptomatic cholelithiasis
History of pituitary irradiation
Pregnancy

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-12-2011
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dostinex
Generic name:	Cabergoline
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nizoral
Generic name:	Ketoconazole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sandostatine
Generic name:	Octreotide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-09-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20862
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2011-003264-77-NL
CCMO	NL37105.078.11