A double blind, randomized, placebo controlled four way cross-over trial to investigate the effects of metoclopramide on central vasopressin release and HPA-axis activation

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Primary:1. To establish the effect of MCP on the release of plasma AVP and subsequent ACTH and cortisol secretion in the absence of a 5HTP-challenge.2. To establish the effect of MCP on the release of plasma AVP and subsequent ACTH and cortisol...

Ethical review	Approved WMO
Status	Pending
Health condition type	Mood disorders and disturbances NEC
Study type	Observational invasive

Summary

ID

NL-OMON31221

Source
ToetsingOnline

Brief title
Metoclopramide effects on vasopressin and HPA-axis.

Condition

- Mood disorders and disturbances NEC

Synonym
depression, unipolar depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: Akzo Nobel (Organon)Orion Pharma,Centre for Human Drug Research

Intervention

Keyword: challenge test, HPA axis, metoclopramide, vasopressin

Outcome measures

Primary outcome

Pharmacodynamic parameters:

1. plasma ACTH;

2. plasma total and free cortisol

3. saliva cortisol;

4. plasma vasopressin;

5. serum prolactin;

6. Symptom Check List, somatization subscale (SCL-90-SOM);

7. Bond and Lader Visual Analogue Scales (VAS) for alertness, mood, calmness

and nausea.

Pharmacokinetic parameters:

1. plasma metoclopramide;

2. plasma 5-HTP.

Endpoints of the study

Primary study endpoints

1. Effect of metoclopramide on plasma AVP release and neuroendocrine response

of cortisol and ACTH (average time profiles) in the absence of the

5-HTP-challenge.

2. Effect of metoclopramide on plasma AVP release and neuroendocrine response

of cortisol and ACTH (average time profiles) in the presence of the

5-HTP-challenge.

3. Effect of MCP combined with the 5-HTP challenge versus the combined effects

of the separate 5-HTP and MCP challenge (average time profiles).

Secondary outcome

Secondary study endpoints:

1. Effect MCP on the release on the release of plasma prolactin in the presence

and absence of the 5-HTP challenge (time profiles, AUC*s).

2. Effect on release of plasma AVP by 5-HTP challenge (time profiles, AUC*s).

3. Effects of MCP, 5-HTP/CBD/granisetron, 5-HTP/CBD/granisetron and MCP on

plasma AVP release.

4. Concentration-effect relationships for AVP, ACTH, prolactin, serum cortisol,

saliva cortisol for MCP, 5-HTP/CBD/granisetron, 5-HTP/CBD/granisetron and MCP

respectively.

5. PK-PD of metoclopramide.

Study description

Background summary

Major depressive disorder is a severely disabling medical illness that is characterized by anhedonia, depressed mood, anxiety, cognitive dysfunction, neurovegetative disturbances, psychomotor retardation or agitation and increased suicide risk. The depressive disorders may be conceived of as being a

dysregulation of the physiological response to stress. Investigation of altered regulation of the hypothalamus-pituitary-adrenal (HPA) axis is therefore one of the main research strategies in depressive disorders. Increased activity of arginine-vasopressin (AVP) might play a role in at least some forms of major depression. AVP together with corticotrophin-release hormone (CRH) plays a central regulatory role in the HPA-axis. These act synergistically on the anterior pituitary to bring about release of adrenocorticotropin (ACTH), which in turn stimulates the adrenal gland to produce cortisol. Recently, studies have suggested that AVP could play a role in the pathogenesis of melancholic depression, either directly or indirectly as a mediator of the HPA-axis. Furthermore, studies performed with desmopressin, a synthetic analogue of vasopressin, suggest that HPA axis regulation in depression shifts from primary regulation by CRH towards a predominant AVP regulation by upregulation of the V3 vasopressin receptor (V3-R). Thus, the development of V3-R-antagonists as antidepressant could be a useful new strategy to treat these severe types of depression. The development of such V3-R-antagonists could benefit greatly from a reliable function test of the vasopressinergic drive and its effects on the HPA-axis in humans. Such a function test could be used to characterize abnormalities in vasopressinergic regulation in different groups of patients, and to examine the effects of drugs acting on this system in healthy subjects and patients. The aim of this study is to develop a challenge test with AVP mediated HPA-axis activation as objective biomarker. Release of AVP by means of a central mechanism leading to ACTH and cortisol release needs to be explored. It has been shown that an anti-emetic agent, the D2-receptor antagonist metoclopramide (MCP), also stimulates AVP-release from the hypothalamus and/or the pituitary as measured peripherally in plasma. However, the nature of the hypothesized central mechanism is not clear yet.

Arginine-vasopressin (AVP) is a physiological co-activator of the HPA-axis, and would therefore be expected to act in the presence of an (endogenous) CRH-stimulus. Under physiological circumstances, the endogenous release of CRH varies considerably, depending on circadian influences and environmental stress factors. Most experiments in healthy volunteers occur in the mid-morning, when HPA-axis activation is significantly lower than during the early morning hours. Under these circumstances, AVP-release by MCP is expected to yield only partial ACTH-activation, leading to a relatively small neuro-endocrine response with a high variability. Recent experiments with systemically administered doses of an desmopressin (dDAVP), provided some indications that vasopressinergic ACTH-release is limited, when endogenous HPA-axis-activity is low. Higher doses of desmopressin were precluded by the well-known systemic cardiovascular and coagulatory effects, so it is possible that higher pituitary AVP levels could have led to larger ACTH/cortisol increases. At any rate, considerably higher increases can be achieved with a recently developed 5HTP-challenge test. The combination of endogenous AVP with the 5HTP-challenge is therefore expected to cause a more sizeable and more reproducible increase in ACTH- and cortisol release, than AVP alone.

Study objective

Primary:
1. To establish the effect of MCP on the release of plasma AVP and subsequent ACTH and cortisol secretion in the absence of a 5HTP-challenge.
2. To establish the effect of MCP on the release of plasma AVP and subsequent ACTH and cortisol secretion in the presence of a 5HTP-challenge.
3. To establish whether the effect of MCP combined with the 5HTP-challenge is larger than the combined effects of the separate 5-HTP and MCP challenges.

Secondary:
1. To establish the effect of MCP on the release of plasma prolactin in the presence and absence of a 5HTP-challenge.
2. To establish whether the serotonergic 5-HTP-challenge could also cause plasma AVP release.
3. To establish the effect of these challenges on the salivary cortisol release.
4. To establish the concentration-effect-relationships for the pharmacodynamic (neuroendocrine) responses.

Study design

Double blind, randomized, placebo-controlled, four-way cross-over trial.

Study burden and risks

Risks:
5-HTP
Single-dose oral administration of 5-HTP can result in short-lasting nausea, vomiting, palpitations and lightheadedness.

Carbidopa
There are no expected side effects of short-term use of carbidopa, although it can intensify the side-effects of 5-HTP.

Granisetron
Granisetron can cause headache, constipation, diarrhoea and sedation.

MCP
Metoclopramide can cause drowsiness, acute extra-pyramidal side-effect (EPS), anxiety and either accelerated absorption or decreased bioavailability for concomitantly administered drugs due to its prokinetic effect. Long term use of metoclopramide may lead to tardive dyskinesia, depression and erectile dysfunction.

Drug-drug interaction effects:
MCP and granisetron may have a synergistic effect on sedation and depression of

the CNS. MCP may cause increased stomache transit time and decreased duodenal transit time. No other pharmacokinetic or pharmacodynamic drug-drug interaction effects for the combinations 5-HTP; CBD; MCP; granisetron are known.

Rare adverse events during the study
As with any medication, rare side effects cannot be excluded beforehand. Occasional reports of the following adverse events have been made:
• 5-HTP may cause dullness and depressed mood.
• Granisetron may rarely cause allergic reactions (varying from rash to anaphylactic reactions) or transient elevation of serum transaminases.
• Hypotension and depression may occur with i.v. use of metoclopramide.

Antidotes:
Adverse events will be treated symptomatically if necessary (paracetamol for headaches, 2mg granisetron p.o. additionally for breakthrough nausea or vomiting).

For 5-HTP and granisetron no specific antidotes exist. Metoclopramide-induced acute EPS (eg. acute dystonia) can be treated with an anti-cholinergic agent eg. biperiden hydrochloride administered either orally or intramuscularly, depending on the severity of the EPS.

Burden:
1. no coffee/tea/chocolate on study days;
2. no smoking on study days;
3. no alcohol 24 hours preceding and during each study day;
4. no excessive physivcal activity (eg. sport) 48 hours preceding every study day;
5. no brushing of teeth on the morning of each study day;
6. tryptophane deficient diet will be supplied. Fluid intake restricted to water and no fruit allowed;
7. 4,5 hours semi-supine on bed to minimalize basal HPA-axis activity on each study day.

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

Age of 18-45 years (extremes included);
Able and willing to sign the Informed Consent Form prior to screening evaluations; Able to refrain from use of all (methyl)xanthines (e.g. coffee, tea, cola, chocolate) from admission at 22h00 prior to each study day and during each stay at the CHDR clinic;
Able to refrain from alcohol use from 24 hours prior to and for the duration of every stay at the CHDR clinic;
Able to refrain from strenuous physical exercise from 48-hours prior to each dosing until dismissal from the CHDR clinic;
No disturbed day/night rhythm due to e.g. working in night-shifts or traveling over time zones within 3 weeks prior to the first dose;
Use of no prescribed drug (especially psychotropic drugs) within two weeks preceding the first dose, excluding paracetamol and certain dermatological preparations (as to judgement of research physician);
Using a current daily average of less than 4 Units alcohol, or maximally consuming less than 6 U alcohol per occasion of alcohol use;
Using a current daily average of less than 4 Units (methyl)xanthines (e.g. coffee, tea, cola, chocolate);
Smoking less than 5 cigarettes per day;
No past or present recreational use of methamphetamines, MDMA or *ecstasy*;
No history of drug sensitivity.

Exclusion criteria

A body mass index (BMI) of less than 18 or more than 28 (extremes included) and a body weight of less than 60 kg;
(History of) physical and mental illness as determined by history taking, physical and laboratory examinations, ECG and vital signs recordings;
Clinically significant pulmonary, cardiac, renal, hepatic, neurological (including epilepsy), endocrinological or gastrointestinal disease;
History of movement disorder (including movement disorder due to D-antagonists);
Past or present clinically significant DSM-IV psychiatric disorder and/or substance abuse disorder, as diagnosed by GP or psychiatrist;
Parents, children or siblings with a psychiatric disease as diagnosed by GP or psychiatrist;
Use of illicit drugs within two weeks prior to screening;
Positive drug (morphine, benzodiazepines, cocaine, amphetamine, THC, metamphetamines, MDMA) or alcohol screen at screening and or/admission;
Blood donation within 90 days prior to the first dose;
Participation in an investigational drug study within 90 days prior to the first dose, or in four studies (or more) in the past year;
Positive test result on hepatitis B surface antigen or hepatitis C antibodies;
Positive test result on HIV 1/2 serology

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	27-03-2007
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Kytril
Generic name:	granisetron
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Levotonine
Generic name:	5-hydroxytryptophane (oxitriptan)
Product type:	Medicine
Brand name:	Maxolon
Generic name:	metoclopramide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sinemet
Generic name:	carbidopa/levodopa
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-03-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-05-2007
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-07-2007
Application type:	Amendment

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	EUCTR2006-005907-32-NL
CCMO	NL16525.058.07