Randomized, double-blind, placebo-controlled trial to evaluate the efficacy of continuous subcutaneous apomorphine infusion in Parkinson*s disease patients with refractory visual hallucinations

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To investigate the efficacy of continuous subcutaneous apomorphine infusion compared to placebo in PD patients with visual hallucinations.

Ethical review	Approved WMO
Status	Pending
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON45825

Source
ToetsingOnline

Brief title
Apomorphine in PD patients with visual hallucinations: a RCT

Condition

- Movement disorders (incl parkinsonism)

Synonym
parkinsonism, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Mosafarma

Intervention

Keyword: Apomorphine, Parkinson's disease, Visual hallucinations

Outcome measures

Primary outcome

The primary endpoint of this trial is the subjective impression of severity

measured with CGI-S.

Secondary outcome

Secondary study endpoints are:

• Change in symptoms of visual hallucinations measured with the NPI-Q.

• Subjective impression of improvement measured with CGI-I.

• Change in cognition measured with MoCA.

• Change in sleeping problems measured with PDSS-II.

• Change in depression and anxiety measured with HADS.

• Change in apathy measured with AS.

• Change in motor function measured with MDS-UPDRS III, IV and V.

• Change in visual perception measured with VOSP battery.

• Change in attention measured with TAP.

• Change in symptoms of visual hallucinations measured with VHQ.

Safety endpoints are:

• Change in blood pressure (e.g. orthostatic hypotension).

• Occurrence of side effects.

Study description

Background summary

Visual hallucinations occur frequently in Parkinson*s disease (PD). The prevalence of visual hallucinations ranges from 22 to 38% (Fénelon and Alves, 2010), increasing after long-term follow-up to more than 60% (Goetz et al., 2010). The occurrence of visual hallucinations is predictive for progression to more severe forms of PD psychosis and development of PD dementia (Fénelon and Alves, 2010) reducing quality of life (Gibson et al., 2013). Risk factors for visual hallucinations are older age (Fénelon and Alves, 2010; Gallagher et al., 2011), longer disease duration (Fénelon and Alves, 2010; Gallagher et al., 2011; Kalaitzakis et al., 2009), disease severity (Gallagher et al., 2011), and cognitive impairment (Gallagher et al., 2011). Visual hallucinations are associated with sleeping problems, depression and anxiety (Gibson et al., 2013).

The genesis of visual hallucinations in PD is related to impaired visual processing. Collerton and colleagues have proposed the perception and attention deficit (PAD) model, suggesting that visual hallucinations are caused by disruption of either the bottom-up and/or top-down visual processing (Collerton et al., 2005). Impaired bottom-up and top-down visual processing in patients with PD and visual hallucinations is supported by structural and functional imaging (Lenka et al., 2015; Meppelink, 2015), and clinic-pathological studies (Gallagher et al., 2011; Harding et al., 2002; Kalaitzakis et al., 2009; Papapetropoulos et al., 2006). Higher cortical visuoperception and attention are impaired in PD patients with visual hallucinations compared to their PD patients without visual hallucinations (Barnes et al., 2003; Gallagher et al., 2011; Grossi et al., 2005; Meppelink et al., 2008; Ramírez-Ruiz et al., 2008). The PAD model linked the genesis of visual hallucinations in PD to cholinergic dysfunction (Collerton et al., 2005). However, it is suggested that dysfunctional mono-amine neurotransmitters could also be linked to the occurrence of visual hallucinations.

In treating visual hallucinations very few therapeutic options are available in PD. The use of classic anti-psychotics is complicated by their extra-pyramidal side effects. Some atypical anti-psychotics like quetiapine and clozapine do not worsen parkinsonism and are now being most used. Only clozapine has been shown to be efficacious in randomized controlled trials, and is therefore considered as first choice (Ballard et al., 2013). However, the use of clozapine is associated with an increased risk of agranulocytosis (Ballard et al., 2013; Seppi et al., 2011), requiring careful follow-up of leucocytes. So treatment options are limited and cumbersome, stressing the need of alternative

therapies.

An alternative therapeutic option might be continuous apomorphine infusion (CAI). CAI is now being used successfully in PD patients with motor fluctuations. In contrast to other dopamine agonists, apomorphine is well-tolerated in advanced PD patients with visual hallucinations (Borgemeester et al., 2016). Moreover, there is growing anecdotal evidence that CAI may improve non-motor symptoms, such as visual hallucinations (Borgemeester et al., 2016; García Ruiz et al., 2008; Martinez-Martin et al., 2011, 2015).

Two studies have investigated the role of apomorphine on visual hallucinations in PD patients in particular. Ellis and colleagues showed that 12 PD patients of whom 8 with visual hallucinations and 2 with confusion, had no worsening of psychotic symptoms after initiation of apomorphine treatment (Ellis et al., 1997). Above that, in most patients hallucinations disappeared completely, even after long-term follow-up (range 8-72 months). The efficacy of apomorphine on visual hallucinations is investigated in one small open-label trial (van Laar et al., 2010). After a follow-up of six weeks, a significant improvement on the neuropsychiatric inventory questionnaire was shown in eight PD patients with visual hallucinations. In summary, apomorphine is suggested to have a beneficial effect, however the number of patients is limited and both studies lacked a control group.

The suggested beneficial effect of apomorphine could be linked to the piperidine moiety incorporated in the structure of apomorphine and other anti-psychotics (van Laar et al., 2010). The piperidine moiety has specific binding sites with dopaminergic and serotonergic receptors (Nematollahi et al., 2014), possible related to the potential anti-hallucinogenic effect of apomorphine.

Study objective

To investigate the efficacy of continuous subcutaneous apomorphine infusion compared to placebo in PD patients with visual hallucinations.

Study design

This study is designed as a randomized, placebo-controlled, double-blind trial. Subjects will be matched by age and cognition.

Intervention

Patients will be treated with either apomorphine 5 mg/ml or placebo (saline) for four weeks.
Apomorphine will be infused subcutaneously during the waking day using a apomorphine pump.

Titration of apomorphine will be conducted by telephone contact.

Study burden and risks

Benefit
The benefit lies in the possibility of a positive therapeutic effect on visual hallucinations, and with their participation subjects will contribute to the scientific understanding of apomorphine in patients with PD and visual hallucinations.

Risks
The main risk for subjects is related to the use of apomorphine. Apomorphine will be used off-label. Based on previous experience with apomorphine, a common side effect is the development of subcutaneous nodules. Other side effects are rare, but more serious and adequate measures are known and provided.

Burden
In this randomized, placebo-controlled trial subjects have to visit the out-patient clinic three times (i.e. a screening, baseline and follow-up visit). At screening, a blood sample and ECG will be performed. Before initiation of apomorphine or placebo, subjects will be pre-treated with domperidone 10 mg tid to avoid peripheral side effects of apomorphine such as nausea and orthostatic hypotension. Several questionnaires will be filled out at baseline and at follow-up. The burden for subjects is kept low given the short study duration of only four weeks.

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

• Female and male subjects aged >=30;
• Diagnosis of clinical established PD, defined by the MDS-PD criteria (Postuma et al., 2015);
• Presence of visual hallucinations, defined as minimal 1 time a week;
• Visual hallucinations must have developed after PD diagnosis;
• Visual hallucinations must have been optimally treated with reduction of dopamine agonists, if appropriate;
• Female subjects must complaint with a highly effective contraceptive method (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method) during the study, if sexually active;
• Subjects should be able and capable of adhering to the protocol, visit schedules, and medication intake according to the judgement of the investigator.

Exclusion criteria

• Symptomatic, clinically relevant and medically uncontrolled orthostatic hypotension;
• Patients with a prolonged QT interval corrected for heart rate according to Bazett*s formula (QTc) of >450 ms for male and >470 ms for female at screening, or history of a long QT syndrome;
• PD medication change (i.e., dopamine-agonists, amantadine, MAO-B inhibitor, anticholinergics and cholinesterase inhibitors) in last month prior to initiation (van Laar et al., 2010);
• Active psychosis or a history of significant psychosis;
• Any medical condition that is likely to interfere with an adequate participation in the study including e.g. current diagnosis of unstable epilepsy, clinically relevant cardiac dysfunction and/or myocardial infarction or stroke within the last 12 months.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2016
Enrollment:	35
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	APO-go
Generic name:	Apomorphine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-11-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-11-2016
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2016-000102-11-NL
ClinicalTrials.gov	NCT02702076
CCMO	NL55949.042.16