Treatment of apomorphine-induced skin reactions: a pilot study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Administration site reactions
Study type	Interventional

Summary

ID

NL-OMON41221

Source
ToetsingOnline

Brief title
Treatment of apomorphine-induced skin reactions: a pilot study

Condition

- Administration site reactions
- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Apomorphine, Skin reactions, Subcutaneous nodules, Treatment

Outcome measures

Primary outcome

The effect of each treatment option will be evaluated by changes in global perceived effect (GPE).

Secondary outcome

Changes in nodule size;

Changes in erythema size;

Changes in histologic skin tissue characteristics;

Other study parameters:

Eosinophilia will be measured to investigate a systemic allergic reaction.

Allergic predisposition in the development of skin reactions, personal and family history of allergies and atopic constellation will be questioned.

Study description

Background summary

Levodopa as gold-standard treatment of Parkinson*s disease (PD) is associated with the occurrence of motor complications in the long term. After 5 years of levodopa treatment 50% of the patients develop motor response fluctuations and dyskinesia, and 80% after 10 years (Chase et al., 1993; Schrag & Quinn, 2000). Continuous infusion of apomorphine has shown to be very efficacious in treating these motor response fluctuations and dyskinesia (Fox et al., 2011). However, a common side effect of apomorphine infusion is the formation of subcutaneous nodules (Deleu et al., 2004). It may cause distress due to discomfort such as redness, itchiness or tenderness (van Laar et al., 1998). Subcutaneous nodules interfere with the absorption rate and may cause *flip-flop* kinetics (Neef &

van Laar, 1999), which limits the duration and effectiveness of apomorphine.

The histopathology of the nodules is poorly understood. Four studies were found performing biopsies of subcutaneous nodules induced by continuous subcutaneous apomorphine infusion (Stibe et al., 1988; Acland et al., 1998; van Laar et al., 1998; Pot, 2005) of which only two performed multiple biopsies (Acland et al., 1998; van Laar et al., 1998). Acland and coworkers (1998) took biopsies in ten patients from lesions resulting from the previous day*s infusion site. Six out of ten biopsies showed a predominantly eosinophilic infiltrate into the subcutaneous fat. Van Laar and coworkers (1998) took multiple biopsies in three patients varying from 1 to 14 days after termination of continuous subcutaneous apomorphine infusion. The biopsies showed an infiltrate, which was loaded with melanin-like pigment. This pigment was supposed to be related to quinone breakdown products of apomorphine. Apomorphine is auto-oxidized into o-quinones. O-quinones can undergo conjugation reactions or can be polymerized into dark melanin-like pigments (van Laar et al., 1998). The contribution of o-quinones to nodule formation is not known. The formation of nodules was considered to be a hypersensitivity reaction either of a delayed type IV or a late form of the immediate type I reaction (Acland et al., 1998; van Laar et al., 1998). Apomorphine as a derivative of morphine and having a close structural similarity to morphine, could have the same allergenic properties as morphine (van Laar et al., 1998). Patch testing did not support a type IV hypersensitivity reaction, which could have been the result of an insufficient concentration of apomorphine (Acland et al., 1998).

Since the histopathology of the nodules is poorly understood, treatment options are limited and suggestive. Authors suggested the use of ultrasound, massage, the use of silicon patches and 50% dilution of apomorphine with 0.9% normal saline to significantly reduce nodule formation (Bowron et al., 2004; Deleu et al., 2004; Colzi et al., 1998; Lees et al., 2002; Poewe & Wenning, 2000). Only the use of ultrasound has been studied in a small-sample randomized controlled trial which showed a beneficial effect on tenderness and hardness compared to a sham ultrasound, however this did not reach significance (Poltawski et al., 2009). In the Netherlands, the use of ultrasound is not integrated in the treatment of apomorphine-induced skin reactions for practical reasons.

The University Medical Center Groningen (UMCG) uses massage, dilution and hydrocortisone administration, dermally or subcutaneously, in the treatment of apomorphine-induced skin reactions. However, evidence for one of these treatment options is lacking. Neither the benefits nor the risks have been part of research. The planned pilot study is intended to investigate the efficacy of these treatment options to provide such evidence.

Study objective

The primary objective of this pilot study is to determine the effectiveness of four treatment options for local skin reactions induced by continuous

subcutaneous apomorphine infusion, as compared to no treatment.
The primary endpoint is the measured absolute change on the global perceived effect (GPE) scale after treatment with one of these options.
The secondary objective of this study is to investigate the role of allergy in these apomorphine-induced skin reactions.
Secondary endpoints are therefore changes in nodule and erythema size, changes in histological skin tissue characteristics (presence of eosinophils, melanine-like pigment, fibrosis, macrophages, histiocytes and lymphocytes), extend of eosinophilia, personal and family history of allergies and atopic constellation.

Study design

This pilot study is designed as an open label crossover trial of four treatments in a fixed sequence in 20 PD patients showing skin reactions to continuous subcutaneous apomorphine infusion. The study will comprise 1 screening visit to confirm subjects* eligibility. The duration of inclusion is 6 months. The sequence of treatments for each patient eligible will be administered over a period of 4 months. The overall duration of the study is four months + one week. All patients receive four therapeutic interventions, each with a duration of 14 days. After each period of two weeks two deep punch biopsis will be taken to assess the secondary endpoints, one biopsis of a lesion treated for three days and one biopsis of a lesion after being treated for two weeks.

Intervention

The investigational treatment options are part of the current standard treatment of skin reactions in Parkinson*s disease patients treated with continuous subcutaneous apomorphine infusion. Subjects are standard instructed to take the following measures:
• Strict hygiene;
• Daily rotation of insertion site, making use of the whole abdominal wall.

The investigational treatment options will be given in a fixed sequence:
1. Massage: Start massage of nodule with a spikey ball. Massage nodules three times a day for 2 minutes. After 14 days, determine nodule size and erythema size of lesions treated for 3 and 14 days, take a picture with scale of lesions and whole abdominal skin. Perform a deep punch biopsy of nodules after 3 and 14 daysof treatment and take blood sample. Administer global perceived effect (GPE) scale;
2. Topical administration of hydrocortisone: Start with treatment of the nodule with hydrocortisone cream 1% 1 time a day. After 14 days, determine nodule size and erythema size of lesions treated for 3 and 14 days, take a picture with scale of lesions and whole abdominal skin. Perform a deep punch biopsy of nodules after 3 and 14 days of treatment and take blood sample. Administer GPE

scale;
3. Dilution: Start dilution of apomorphine. Dilute apomorphine 0.5% (5 mg/ml) to 0.25% (2.5 mg/ml) by addition of same volume 0.9% NaCl (physiological saline). After 14 days, determine nodule size and erythema size of lesions treated for 3 and 14 days, take a picture with scale of lesions and whole abdominal skin. Perform a deep punch biopsy of nodules after 3 and 14 days of treatment and take blood sample. Administer GPE scale;
4. Subcutaneous administration of hydrocortisone: Start with pre-treatment with Solu-Cortef 10mg. After 14 days, determine nodule size and erythema size of lesions treated for 3 and 14 days,take a picture with scale of lesions and whole abdominal skin. Perform a deep punch biopsy of nodules after 3 and 14 days of treatment and take blood sample. Administer GPE scale.

Study burden and risks

Risks
Apomorphine-induced skin reactions may be the result of an allergic reaction (Acland et al., 1998; van Laar et al., 1998). Safety endpoints include evaluation of liver enzymes to anticipate on a chronic allergic reaction which is potentially harmful. Eventually, patients need to stop apomorphine treatment.
The extra invasive procedures (i.e. deep punch biopsies and blood samples at each visit) are considered as low risk procedures. The risk of bleeding is minimal even when using anti-coagulantia.

Benefits
For the patients the benefit lies in the possibility of a therapeutic effect, and with their participation in the trial all patients contribute to a scientific understanding and treatment of apomorphine-induced skin reactions.

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 idiopathic Parkinson*s disease of >3 years* duration, defined by the UK Brain Bank criteria, with the exception of >1 affected relative being allowed, without any other known or suspected cause of Parkinsonism (Gibb & Lees, 1988);
• Treatment with continuous subcutaneous apomorphine infusion;
• Presence of apomorphine-induced skin reactions (i.e. erythema, swelling and/or subcutaneous nodule formation;
• Male and female patients must be compliant 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 schedule, and medication intake according to the judgement of the investigator.

Exclusion criteria

• High suspicion of other parkinsonian syndromes;
• History of respiratory depression;
• Hypersensitivity to hydrocortisone or any excipients of the medicinal product;
• Concomitant therapy with histamine antagonist or (gluco)corticosteroids;
• Presence of Cushing*s disease or hypercortisolism;
• 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;
• Pregnant and breastfeeding women;
• Current infectious disease with fever at the time of investigation.

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):	26-10-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	APO-go
Generic name:	Apomorphine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Hydrocortisone cream10 mg/g FNA Fagron
Generic name:	Hydrocortisone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Solu-Cortef
Generic name:	Hydrocortisone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	11-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-06-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-02-2017
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	EUCTR2014-000657-36-NL
ClinicalTrials.gov	NCT02230930
CCMO	NL46934.042.14