Treatment with apomorphine in patients with Parkinson's disease

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Parkinson´s disease (PD)-patients with unacceptable motor fluctuations or treatment resistant tremor should be referred to a Movement Disorders Clinic where a comprehensive and unbiassed evaluation can be made by a neurologist specialized in movement disorders with a vast experience of adjusting peroral medication and in the use of deep brain stimulation (DBS), continuous subcutaneous administration of apomorphine, and continuous intestinal administration of levodopa.

Background:

Apomorphine is, together with Levodopa, the most effective symptomatic pharmacologic treatment against PD motor symptoms (Review: 1, 2, 3). The effect of these drugs on motor symptoms is quantitatively and qualitatively comparable, but the pharmacokinetics are considerably different (4). The subcutaneous absorption rate of apomorphine is fast and peak plasma concentrations is typically reached after 5 minutes and the clinical effect after a mean of 7-8 minutes. The biological half-life in elimination phase is approximately 33 minutes and the effect duration about 60 minutes. The minimal effective dose of apomorphine is individual and must be titrated for each patient.

A. Apomorphine Injections (Ref. 5-8)

Indications for intermittent injection with apomorphine pen

- Clinically relevant off periods despite optimized oral treatment AND
- Few or irregular off periods

The best chance of a good effect is found in relatively young and active patients with normal cognitive functions and irregular "wearing off". However, in young patients, there might be a risk of priming dyskinesias by pulsatile treatment (9).

Situations when apomorphine injections may be helpful

- Unacceptably long duration of morning off
- Difficulties in gait initiation
- Patients who are strongly dependent on fast and reliable symptom relief when off
- Patients on continuous infusion with apomorphine or Duodopa, who have difficulties starting the infusion pump without assistance during morning off.
- End-stage parkinsonian patients in care facilities, for whom small doses up to 5 times a day or night reduce the risk of falling and facilitate ambulation (injection to be given by trained staff)
- To reduce unpredictable or severe off related problems with swallowing, urinary voiding, defecation, dystonia and pain.
- To give a feeling of freedom – knowing that the pen is at hand and can be used when necessary
- Prior to and during (DBS) surgery, to allow for ambulation and comfort. Post operative care.
- Occasionally, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) may transiently benefit from

injection for particular symptoms (e.g., swallowing, mobility).

Other prerequisites

- Patient or caregiver have to understand the symptoms and when to give the injection.
- Adequate training of patients and caregivers must be possible.
- Availability of support for training, consultation and general education of patients and care-givers, e.g. by a specialized nurse.
- Domperidone is generally used to reduce nausea when apomorphine treatment is initiated but should be tapered down within a week or as soon as possible due to the risk of QT-prolongation.

Contraindications

- Pronounced dyskinesias
- Pronounced orthostatism
- Strong tendency to hallucinations and psychotic side effects or hypomania
- Clinically significant dementia precluding the ability to understand the treatment and its effects.
- History of intolerance to apomorphine
- Severe cardiovascular disease
- Severe renal insufficiency
- Severe hepatic insufficiency
- Pregnancy and lactation.
- Previous history of dopamine dysregulation syndrome (13)

Advice on treatment initiation

Apomorphine test

The purpose of the test is to determine if the patient has a meaningful effect of apomorphine and to make a rough dose titration.

Preparations: An ECG should be performed to exclude QT-prolongation prior to starting pre-treatment with domperidone. To reduce the risk of nausea, pre-treat for 2-3 days with domperidon 10 mg TID. Levodopa is discontinued the evening before the apomorphine test.

Test execution: 1 mg of apomorphine is injected s.c. and effect and side effects are noted. This is repeated with time intervals of ½-1 hour with dose increases in steps of 1.5 mg at a time until a good clinical effect, or unacceptable side effects are observed. Normally it is not advisable to give more than 7-8 mg of apomorphine.

Treatment start: The initial therapeutic apomorphine injection dose when the patient leaves the clinic is recommended to be half the threshold dose found during an apomorphine test.

If apomorphine is started without an apomorphine test, it is advisable to start with an injection of 1 mg apomorphine sc. The following apomorphine injection doses are then increased, typically with 0.5-1 mg/day, until an optimal dose is reached. The optimal dose (typically 2-4 mg) would be the lowest apomorphine dose, which produces a "full" antiparkinson effect. The injections are administered into the patient's lower abdomen or outer thigh upon the first signs of an "off" episode. Domperidone (10 mg TID) is given three days before and during the first days of treatment after which it can be tapered off in most patients. The patients are instructed to recognize early signs or symptoms of "off" periods, and to inject as soon as such symptoms appear, but with a limit on the number of injections per day of approximately 4-5. The patient's other oral medication is normally kept unchanged.

Safety monitoring: Drug induced haemolytic anemia is a rare adverse effect of apomorphine. It can develop at any time after treatment initiation and the patient should be informed about acute symptoms of haemolysis, like pallor, dark urine, fatigue and shortness of breath. Hemoglobin levels should be checked regularly and if anemia is suspected. In case of anemia, drug induced haemolytic mechanism should be considered and a direct antiglobulin test (Coomb's test) be performed. An ECG should be performed before and after a week of treatment, as well as when a stable apomorphine use has been achieved, to check for QT-prolongation. This is particularly important if the patient is being treated with domperidone, as both apomorphine and domperidone can prolong the QT-time.

Side effects of apomorphine injection therapy

The most common side effect is a local reaction at the injection site; however, this is rarely of clinical significance (12). Ultrasound seems to be effective in treating the nodules (11). Note that ultrasound treatment is contraindicated in patients treated with deep brain stimulation and cardiac pacemaker. Nausea occurs in about 15% of the patients but can in most cases be effectively treated with domperidone, and usually disappears with continued therapy. Patients injecting themselves at a low frequency may experience more problems with nausea and orthostatic hypotension. A short period of sedation after an apomorphine injection is relatively common. In rare cases hallucinations can be induced and the risk for this seems to be related to the total amount given and the frequency of the injections. In most cases, symptoms of psychosis quickly reversed after cessation of apomorphine. Even more rare side effects include sleep problems, confusion, eosinophilia, rhinorrhea, diarrhoea and vertigo. "Sleep attacks" have been reported in a few cases. Effects on libido and erectile function have not been well-monitored so far. In case of a history of dopamine dysregulation syndrome, the initiation of intermittent apomorphine is contraindicated. It is not yet known if apomorphine may result in a dopamine dysregulation syndrome, but patients with the profile for this syndrome (younger males with a history of abuse or pathological gambling) should be closely monitored for any such development. A need for increased number of injections or increasing dosages per injection is a cause of concern. If the number of injections exceeds 5 per day the patient should be monitored more closely, and continuous infusion should be considered. The side effects that most commonly lead to discontinuation of therapy are nausea, vomiting, dizziness and somnolence.

B. Apomorphine Infusion (Ref. 13-32)

Indications for continuous apomorphine infusion with pump (5mg/mL).

- Advanced Parkinson's disease with pronounced motor fluctuations, not sufficiently treated with oral/patch treatment and who have been found to have a good acute apomorphine response.

The best candidates are young-onset patients with normal cognitive functions and troublesome motor fluctuations.

Special situations that may be successfully treated

- Prolonged or frequent, unpredictable „off" phases
- Troublesome peak-of-dose dyskinesias (22)
- Troublesome bi-phasic dyskinesias (22)
- Need for 5 or more daily sc injections of Apomorphine
- Parkinson-related dystonia
- Extremely difficult cases of RLS (restless legs syndrome), as night time therapy
- Partially levodopa responsive MSA cases (in particular cases with pronounced dysphagia and partial levodopa response)

Other prerequisites

- Adequate in-ward or out-patient training of patients and care-givers must be possible
- Availability of support for training, consultation and general education of patients and care-givers, e.g. by a specialized nurse.

Contraindications

- History of intolerance to apomorphine
- Severe hepatic or renal insufficiency, respiratory or cardiovascular disease
- Pregnancy and lactation
- Pronounced tendency to hallucinations and other psychotic symptoms.
- Severe dementia precluding the ability to understand the treatment and its effects

Relative contraindications

- Cognitive impairment (minor cognitive impairment is allowed contrary to DBS).
- Untreated depression, or patient with (chronic) depressed mode, unless "mental off or apathy" is improved by apomorphine)
- Clinically relevant and severe orthostatism.
- Relevant dermatological disorders
- History of dopamine dysregulation syndrome on intermittent treatment (please see side effects of apomorphine injection therapy).

Advice on treatment initiation-

If the patient is not using several daily apomorphine injections pre-treatment with domperidone 10 mg tid for 3 days prior to the infusion therapy should be considered. Please see "apomorphine injection" for safety monitoring. After reduction of the anti-Parkinson therapy with approximately 50%, the infusion of apomorphine is initiated at a rate of 1 mg/h. This dose is then raised in steps of 0.5-1 mg/h until an optimal effect is achieved. Patients who are already on intermittent injection can often use the injection dose as initial hourly

infusion rate. During titration the infusion dose should not be raised with more than 1 mg/h/day. After this, the titration of the at-demand bolus dose is done in a similar way as in the injection treatment. In-hospital titration for 1-2 weeks can be useful for starting the therapy and educating the patients and caregivers, but with educational support out-patient titration is also possible. After some weeks or months of therapy a further reduction of the oral anti-Parkinson therapy can be tried. About 50% of the patients manage well with apomorphine as mono-therapy. Most patients are treated with day-time treatment only. Apomorphine is given at night time if the night time symptom control is not satisfactory. Nocturnal apomorphine has been reported to improve insomnia in Parkinson´s disease (24). Apart from effects on "off" symptoms, an antidyskinetic effect of apomorphine is now well established (25). The best effects are often seen in patients who can manage on apomorphine monotherapy (26).

Side effects of apomorphine infusion therapy

The most common side effect of infusion therapy is the formation of local noduli and skin irritation, occurring in almost all users (27,30,31). Ultrasound seems to be effective in treating the nodules. Please note that ultrasound treatment is contraindicated in patients treated with deep brain stimulation and cardiac pacemaker. To reduce the formation of nodules, if they are bothersome, higher concentrations than 5 mg/ml apomorphine should be avoided and the infusion site should be changed at least twice per day. There are reports that infusion at the upper part of the back causes less skin reactions. Although hallucinations and other dopaminergic-psychotic side effects can occur, the risk is not higher than with other Parkinson therapies. Haemolytic anaemia may occur (32) – for safety monitoring see apomorphine injections.

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