Treatment with apomorphine in patients with Parkinson's disease

A Scandinavian Movement Disorder Society, ScandModis consensus document

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Parkinson´s disease (PD)-patients in the advanced stage of the disease with an unacceptable motor control 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 L-dopa, 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 relatively constant intraindividually, but varies considerably interindividually and must be titrated for each patient separately.

A. Apomorphine Injections (Ref. 5-8)

Indications for intermittent injection with apomorphine pen

- Clinically relevant off periods in spite of optimized oral treatment
- Good Apomorphine response

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

- Unacceptable long duration of morning off's
- Difficulties in gait initiation
- Bi-phasic dyskinesias
- Patients who are dependent on a reliable effect within a given time
- To patients on continuous infusion with apomorphine or Duodopa, to be able to start pump infusion in the morning without assistance.
- 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 off related problems with swallowing, urinary voiding, defecation 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
- As a diagnostic test (10)

- Occasionally, patients with dystonia, 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
- Ideally a specialized nurse should be available for training, consultation and general education of patients and care-givers
- Motilium (domperidone) is generally given at start, and should be tapered down within a week or as soon as possible due to the risk of QT-prolongation..

Exclusion criteria

- 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.
- Previous history of intolerance to apomorphine
- Severe cardiovascular disease
- Severe renal insufficiency
- Severe hepatic insufficiency
- Pregnancy and lactation.
- Previous history of dopamine dysregulation syndrome (11)

Start of treatment

Apomorphine test

Purpose of the test is mainly to evaluate the effect of apomorphine.
2-3 days prior to test start p.o. domperidon 10 mg TID. Antiparkinsonian drugs with a long half-life are discontinued in time for the medication to be washed out at the time of test. L-dopa is discontinued the evening before the apomorphine test.
1 mg of apomorphine is injected s.c., while effect and side effects are noted. This is repeated with time intervals of ½-1 hour with apomorphine dose stepwise increased with 1.5 mg, to a good clinical effect, or unacceptable side effects. Normally it is not advisable to give more than 7-8 mg of apomorphine.

When initiating sc apomorphine therapy, Coomb´s test should be performed, and then repeated every 6 months. If the patient is being treated with domperidone, an ECG should be performed before and after a week of treatment and later every 2 to 4 weeks, to check for QT-prolongation. The patient's other oral medication is normally kept unchanged. The initial therapeutic apomorphine injection dose is recommended to be half the threshold dose found during an apomorphine test.

Initiation of apomorphine injection therapy without prior apomorphine test
If no apomorphine test has been performed, it would be 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 ie. approximately 4-5.

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 (anden behandling nu?) seems to be effective in treating the nodules (13). 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 if the therapy is continued. 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. 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. The side effects that most commonly lead to discontinuation of therapy are nausea, vomiting, dizziness and somnolence.

B. Apomorphine Infusion (Ref. 13-30)

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

- Advanced Parkinson's disease with pronounced motor fluctuations, not sufficiently treated with oral/patch treatment
- Good 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 more than 5 daily sc injections of Apomorphine
- Dystonia
- Patients at risk for premature sick leave / retirement, or risk of losing social contacts and normal activity of daily life
- Patients excluded from DBS
- Extremely difficult cases of RLS (restless legs syndrome), as night time therapy
- Partially L-dopa responsive MSA cases (for example cases with pronounced dysphagia)
- Effect on non-motor symptoms?

Other prerequisites

- Adequate in-ward or out patient training of patients and care-givers must be possible
- Ideally specialized nurses should be available for training, consultation and general education of patients and caregivers.

Exclusion criteria

- Previous history of intolerance to apomorphine
- Severe hepatic or renal insufficiency, respiratory or cardiovascular disease
- Pregnancy and lactation
- Pronounced tendency to hallucinations and other psychotic side effects
- Severe dementia precluding the ability to understand the treatment and effects
- Previous history of dopamine dysregulation syndrome on intermittent treatment (please see side effects of apomorphine injection therapy).

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

Start of therapy

The patient should be pretreated with domperidone 10 mg tid for 3 days prior to the infusion therapy. Please see "apomorphine injection" for 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. 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. For starting the therapy and educating the patients and caregivers in-ward, 1-2 weeks of in-hospital titration is usually necessary. 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). 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 occurs in about 3% of the users and a Coomb´s test is advised to be performed before treatment is started and every 6-month.

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