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Treatment with Apomorphine in patients with Parkinson's disease

A Scandinavia Movement Disorder Society, ScandModis consensus document

PD-patients in the advanced stage of the disease with troublesome motor problems in spite of optimal per oral treatment which may include subcutaneous apomorphine injectionsshould be referred to a Movement Disorders Clinic where a comprehensive and unbiased 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.
If this evaluation results in a recommendation of pump therapy, this treatment can be initiated by the referring centre, if adequate resources and experience is at hand. If pump therapy is initiated at a Movement Disorder Centre, the patient may be referred back to the local hospital in 1-2 years time, when the patient is expected to be stable.

Background:

Apomorphine is, together with L-dopa, the most effective symptomatic medical treatment against Parkinson motor symptoms (Review: 1, 2, 3). The motor effect of these drugs are quantitatively and qualitatively comparable, but the pharmacokinetics are considerably different (4). A sub cutaneous injection of Apomorphine has a half-life in distribution phase of about 5 minutes, leading to a 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 "wearing-off"-type fluctuations. However, in young patients, there might be a risk of priming dyskinesias by pulsatil treatment (9).

Situations when Apomorphine injections may be helpful

- Difficulties in gait initiation
- Bi-phasic dyskinesias
- Patients who are (professionally) 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, 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 tests (10)
- Occasionally patients with dystonia, MSA and 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 care-givers must be possible
- Ideally a specialized nurse should be available for training, consultation and general education of patients and care-givers
- Motilium (domperidone) is given at start, and can usually be withdrawn within 3 months (at least in patients taking >2 injections per day).

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

Can be performed in a number of ways.

3 days prior to test start per oral domperidone 10 mg TID.

1. Antiparkinson 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.
2. Unchanged oral treatment. Start with Apomorphine test during severe off period or during freezing.

1 mg of Apomorphine is injected s.c., while effect and side effects are noted. Orthostatic blood pressure is monitored 15 min after injection. This is repeated with time intervals of 1-1 ½ hour with Apomorphine dose stepwise increased with 1-1.5 mg, to a good clinical effect, or unacceptable side effects. Normally it is not relevant to give more than 7-8 mg of Apomorphine.At the start of sc apomorphine therapy, Coomb´s test should be performed. The initial therapeutic apomorphine injection dose is recommended to be the dose with best effect, found during the Apomorphine test. If no Apomorphine test has been performed, it would be advisable to start with an Apomorphine test. 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 around 2-4 mg) would be the lowest Apomorphine dose, which produces a "full" antiparkinson effect. The bolus dose should be 40-50% of the continuous dose. 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 tree days before and during

the first days of treatment after which it in most patients can be tapered off. Due to reports on cardiac problems related to domperidone treatment, an ECG is recommended before starting domperidone. If it is necessary to continue domperidone more than a few weeks, it is recommended to monitor ECG for S-T elongation every 1 to 2 weeks. 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.

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 (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, such a psychosis is 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 closely be monitored for any such development. Increased number of injections or increasing dosages per injection is 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. 13-27)

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

- Advanced Parkinson's disease with pronounced motor fluctuations
- Severe disease not sufficiently treated with oral/patch treatment
- Patients with troublesome fluctuations in spite of optimized oral 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 loosing 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)

Other prerequisites

- Adequate in-ward 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 hepar or renal insufficiency, respiratory or cardiovascular disease
- Pregnancy and lactation
- Pronounced tendency to hallucinations and 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, provided "mental off or apathy" is ruled out (improved by Apomorphine)
- Clinically relevant and severe orthostatism.

Start of therapy

Reduce the following per oral medication with 50%: short acting dopamine agonists, amantadine and anticholinergics, 2-3 days before infusion start. Stop treatment with dopamine agonists with slow release formula, MAO-B inhibitors and COMT inhibitors are discontinued

at infusion start. The infusion of apomorphine is started 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, 2-4 weeks of in-ward treatment is mostly necessary. It is also possible to start treatment in an out patient setting. 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 first treated with day-time treatment only. For treating nighttime problems a sustained release l-dopa or dopamine agonist patch is usually sufficient. Apomorphine is given nighttime if the nighttime symptom control is not satisfactory despite this. 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. Note that ultrasound treatment is contraindicated in patients treated with deep brain stimulation and cardiac pacemaker. To avoid this, the most important steps are to avoid higher concentration than 5 mg/ml apomorphine and to change infusion site at least twice per day. There are reports that infusion at the upper part of the back causes less skin reactions. Hallucinations and other dopaminergic-psychotic side effects can occur, the risk is, however, not higher than that of 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.

Due to reports on cardiac problems related to domperidone treatment, an ECG is recommended before starting domperidone. If it is necessary to continue domperidone more than a few weeks, it is recommended to monitor ECG for S-T elongation every 1 to 2 weeks.

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