PD-patients in advanced stage of the disease should 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.

Background:

Apomorphine is, together with L-dopa, the most effective symptomatic medical treatment against Parkinson motor symptoms (Review: 1, 2, 3). The anti-parkinsonism effects of these drugs are quantitatively and qualitatively comparable, but the pharmacokinetics are considerably different (4). A sc 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 approximately 60 minutes. The minimal effective dose of apomorphine is relatively constant intra-individually, but varies considerably inter-individually and must be titrated for each patient.

A. Apomorphine Injections (Ref. 5-8)

Indications for intermittent injections with Apomorphine pen

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

Very good clinical effect is seen in relatively young and active patients with normal cognitive functions and “wearing-off”-type fluctuations. However, in the young patients, the risk of priming dyskinesias is probably increased by pulsatile treatment (9).

Clinical situations where apomorphine injections can be useful

- 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 obtain dexterity to cope with starting pump infusion in the morning with out assistance
- End stage parkinsonian patients in care facilities, for whom small doses up to 5 times a day or night may allow independent swallowing, less risk of falls during ambulation (injection to be given by trained staff)
- 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 reduce the discomfort of the pause in per oral medication.
- Post operative care
- In diagnostic tests (10)
• Occasionally patients with dystonia, MSA and PSP may transiently benefit from injection for particular symptoms (e.g. swallowing, mobility, defecation).

Other prerequisites
• Patient or caregiver have to be educated in the symptoms in parkinsons disease and the indication for giving an injection
• Adequate training of patients and care-givers must be possible
• Ideally a specialized PD-nurse should be available for training, consultation and general education of patients and care-givers
• Motilium (domperidone) is administered at start, and can usually be withdrawn within 3 months (at least in patients taking >2 injections per day).

Exclusion criteria
• Pronounced orthostatism
• Strong tendency to hallucinations, psychotic side effects or hypomania
• Clinically significant dementia tampering the ability to understand the treatment and its effects.
• Previous history of intolerance to apomorphine
• Severe cardiovascular disease
• Severe renal insufficiency
• Liver insufficiency
• Pregnancy and lactation.
• Previous history of dopamine dysregulation syndrome (11)

Start of treatment
Apomorphine test
3 days prior to test start p.o. domperidone 20 mg TID. 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. 1 mg of apomorphine is injected s.c., while effect and side effects are noted. This is repeated with time intervals of 1-1 ½ hour with apomorphine dose stepwise increased with 1 mg, to a good clinical effect, or unacceptable side effects. Normally it is not relevant to give more than 7-8 mg of apomorphine.

When starting sc apomorphine therapy, a Coomb’s test should be performed. Other medication is normally continued unchanged. The initial therapeutic apomorphine injection dose is recommended to be half the threshold dose found during an Apomorphine test. If no Apomorphine test has been performed, it would be advisable to start with an injection of 2 mg apomorphine. 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 s.c. into the patient's lower abdomen or outer thigh upon the first signs of an "off" episode. Domperidone (20 mg TID) is given three days before and during the first days of treatment after which it in most patients can be tapered off. The patients are instructed in recognizing early signs or symptoms of "off" periods, and to inject as soon as such symptoms appear, but with a limit set by the doctor of the number of injections per day.

Side effects of Apomorphine injection therapy
The most common side effect is a local irritation at the injection site with formation of subcutaneous nodules; however, this is rarely of clinical significance (12). Ultrasound
treatment seems to be effective in treating the nodules (13). Observe that ultrasound treatment is contra
indicated 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 stopped. Even more rare side effects include sleep problems, confusion, eosinophilia, rhinorrhea, and vertigo due to orthostatic hypotension. "Sleep attacks" have been reported in a few cases. Effects on libido and erectile function have not been well monitored so far. Initiation of intermittent apomorphine is contraindicated in the case of a history of dopamine dysregulation syndrome. 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 this. Factors to be monitored are increased number of injections or increasing dosages per injection. Concern should be raised when the number of injections exceeds 5 per day. 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.
• Severe off-dystonia and or off-pain not effectively treated with l-dopa.

The best effect is seen in young-onset patients with next to normal cognitive function 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 a 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)
• In case of gastro intestinal surgery and a need of parenteral treatment during a longer period

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 liver or renal insufficiency, respiratory or cardiovascular disease
• Pregnancy and lactation
• Pronounced tendency to hallucinations and psychotic side effects
• Dementia affecting the ability to understand the treatment and it effect
• 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 patients with chronic dysthymia, provided off related depression or apathy is ruled out (improved by Apomorphine)
• Clinically relevant and severe orthostatism.
Start of therapy
After reduction of the anti-Parkinson therapy with approximately 50%, the infusion of apomorphine is started at a rate of half the effective dose from the apomorphine-test. 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. To start the therapy and educate the patients and caregivers a 1-2 weeks hospital admission 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 daytime treatment only. Apomorphine is given nighttime if the nighttime 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 nodules and skin irritation. (27). Ultrasound treatment seems to be effective in treating the nodules. Observe that ultrasound treatment is contraindicated in patients treated with deep brain stimulation and cardiac pacemaker. Local massage with a spiky rubber ball has been proven effective in preventing formation of nodules as well. An other strategy is 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 seen with other Parkinson therapies. That is also the case with impulse control disorders. Hyper sexuality however can be more frequent in apomorphine treatment. Haemolytic anaemia occurs in about 3% of the users. Hence a Coomb´s test is recommended to be performed before treatment is started and every 6-month.

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