

# **Apomorphine Treatment in Patients with Parkinson´s disease**

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*DANMODIS; Danish Movement Disorder Society*

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## **Background:**

Together with L-dopa, Apomorphine is the most effective symptomatic medical treatment for Parkinson motor symptoms (Reviews: 1, 2, 3). The effects of these drugs are quantitatively and qualitatively comparable, but the pharmacokinetics is very 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 the elimination phase is approximately 33 minutes and the duration of the effect is 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 (Refs. 5-8)**

### **Indications for intermittent injection with apomorphine pen**

- Clinically relevant “off periods” in spite of optimized oral treatment
- Good L-dopa or apomorphine responsiveness in ”on” state

The best effects are found in relatively young and active patients with normal cognitive functions and “wearing-off”-type fluctuations. However, in young patients, there may be a risk of priming dyskinesias by pulsatile treatment (9).

Special situations in which apomorphine injections may be beneficial

- Difficulties in gait initiation
- Bi-phasic dyskinesias
- Patients who are professionally dependent on a reliable effect within a given time
- Patients on continuous infusion of apomorphine or Duodopa treatment, to enable them to start the pump infusion in the morning without other assistance
- End stage Parkinsonian patients in care facilities, for whom small doses up to 5 times per day or night may allow independent swallowing and reduce the risk of falls during ambulation (injection to be given by trained staff)
- To provide 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
- In diagnostic tests (10)
- Occasionally, patients with dystonia, MSA and PSP may transiently benefit from injections for specific symptoms (e.g. swallowing, mobility).

### **Other prerequisites**

- Patient or caregiver must understand the symptoms and know when to administer the injection
- Adequate training of patients and care-givers

- Ideally a specialized nurse should be available for training, consultation and general education of patients and care-givers
- Motilium (domperidone) is administered at the start of treatment and can usually be withdrawn within 3 months (at least in patients on >2 injections per day).

### **Exclusion criteria**

- Pronounced dyskinesias
- Pronounced orthostatism
- Strong tendency to experience hallucinations and psychotic side effects or hypomania
- Clinically significant dementia that makes it impossible to understand the treatment and its effects.
- Previous history of apomorphine intolerance
- Cardiovascular disease
- Severe renal insufficiency
- Liver insufficiency
- Pregnancy and lactation.

### **Start of treatment**

Coomb's test should be performed at the start of sc apomorphine therapy. The patient's other oral medication normally remains unchanged. The recommended initial therapeutic apomorphine injection dose is half the threshold dose found during an apomorphine test. If no apomorphine test has been performed, it is advisable to start with an injection of 1 mg apomorphine. The subsequent apomorphine injection doses are then increased, typically by 0.5-1 mg/day, until an optimal dose is reached. The optimal dose (typically around 2-4 mg) is the lowest apomorphine dose which produces a "full" antiparkinsonian effect. The injections are administered into the patient's lower abdomen or

outer thigh upon the first signs of an "off" episode. Domperidone (20 mg tid) is given during the first days of treatment and can in most patients be phased out. 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 (11). Nausea occurs in about 15% of patients, but can, in most cases, be effectively counteracted by means of domperidone and usually disappears when treatment has been going on for some time. Patients injecting themselves at a low frequency may experience greater 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 seems to be related to the total amount administered and the frequency of injections. In most cases, such psychotic side effects can be quickly reversed. Less common 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 been poorly investigated. The side effects that most commonly lead to discontinuation of therapy are nausea, vomiting, dizziness and somnolence.

## **B. Apomorphine Infusion (Refs. 11-25)**

### **Indications for continuous infusion of apomorphine with a pump (5mg/mL).**

- Advanced Parkinson's disease with pronounced motor fluctuations
- Disease sufficiently severe to warrant advanced instead of oral/patch treatment
- Patients with troublesome fluctuations in spite of optimized oral treatment
- Good L-dopa or apomorphine response.

The best response is found in young patients with normal cognitive functions but troublesome motor fluctuations.

### **Special situations that can be successfully treated**

- Prolonged or frequent, unpredictable "off" phases
- Troublesome peak of dose dyskinesias (20)
- Troublesome bi-phasic dyskinesias (20)
- Need for more than 5 daily sc injections of apomorphine
- Dystonia
- Patients at risk of premature sick leave/pension, losing social contacts or unable to carry out the normal activities of daily life
- Patients excluded from DBS
- As night time therapy in extremely difficult cases of RLS (restless legs syndrome)
- Partially L-dopa responsive MSA cases (such as cases with pronounced dysphagia)

### **Other prerequisites**

- Adequate in-ward training of patients and care-givers must be possible
- Specialized nurses should ideally be available for training, consultation and the general education of patients and care-givers.

### **Exclusion criteria**

- Previous history of apomorphine intolerance
- Severe liver or renal insufficiency, respiratory or cardiovascular disease
- Pregnancy and lactation
- Pronounced tendency towards hallucinations and psychotic side effects
- Dementia that makes it impossible to understand the treatment and its effects
- Previous history of dopamine dysregulation syndrome during intermittent treatment.

### **Relative contraindications**

- Cognitive impairment (a minor cognitive impairment is allowed in contrast to DBS).
- Untreated depression, or patients with chronic depressed mood, in cases where “mental off or apathy” can be ruled out (as such states are improved by the administration of apomorphine)
- Clinically relevant and severe orthostatism.

### **Start of therapy**

After reduction of antiparkinsonian therapy by around 50%, apomorphine infusion is started at a rate of 1 mg/h. This dose is then increased in 0.5-1 mg/h steps until an optimal effect is achieved. The infusion dose should not be increased by more than 1 mg/h/day. Subsequently, the titration of the on-demand bolus dose is carried out in a similar way to the injection treatment. In order to start the therapy and educate the patients and care-givers, 2-4 weeks of

in-ward treatment is usually required. After some weeks or months of therapy, a further reduction of oral antiparkinsonian therapy can be attempted. About 50% of patients manage well with apomorphine as a mono-therapy. Most patients first receive day-time treatment only. Apomorphine is given at night if night time symptom control is unsatisfactory. Nocturnal apomorphine has been reported to improve insomnia in Parkinson's disease (22). Apart from effects on "off" symptoms, an antidyskinetic effect has been well established (23). The best response is often seen in patients who can manage on apomorphine monotherapy (24).

### **Side effects of apomorphine infusion therapy**

The most common side effect of infusion therapy is the formation of local noduli and skin irritation, which occurs in almost all users (25). The most important preventative steps are to avoid concentrations higher than 5 mg/ml apomorphine and to change the infusion site at least twice per day. It has been reported that infusion sites in the upper back cause less skin reactions. Hallucinations and other dopaminergic-psychotic side effects can occur, although the risk is no higher than that of other parkinsonian therapies. Haemolytic anaemia occurs in about 3% of users. As a result, Coomb's test should be performed before the start of treatment and at 6-month intervals thereafter.

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