Motor and non-motor effects of apomorphine infusion
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Chapter 8

Summary and general discussion
Introduction

Continuous subcutaneous apomorphine infusion (CSAI) has been introduced by Stibe and colleagues in 1987.\textsuperscript{1,2} Since then, apomorphine has been used all over the world in patients with Parkinson's disease (PD) with motor response fluctuations and levodopa-induced dyskinesia, although it has been bypassed in numbers by levodopa-carbidopa intestinal gel (LCIG), which was just introduced in 2004. The extensive experience has led to numerous publications and observational studies with CSAI, but only recently level I evidence on the clinical efficacy and tolerability of CSAI was shown in the TOLEDO study, a randomized placebo-controlled trial,\textsuperscript{3} with a stable effect over a follow-up period of 12 months.\textsuperscript{4}

However, real-world data on long-term safety and efficacy of CSAI in PD patients were limited, especially in older PD patients with comorbid cognitive dysfunction, visual hallucinations and/or orthostatic hypotension, who were not represented in the published studies. For that reason this PhD thesis was started. Below, our real-world data on the use of apomorphine will be discussed in a broader perspective. In addition, the scope of this thesis was to elaborate on two other topics. Firstly, the controversial relation between the use of apomorphine in PD patients and visual hallucinations, and secondly, apomorphine-related skin problems and providing an evidence-based approach to patients with subcutaneous nodules.

The general discussion provides a summary of main findings of the chapters, after which the findings of the chapters will be integrated with the existing knowledge. In the final part of this thesis, general considerations and future perspectives will be discussed.

Summary of main findings

In chapter one a general introduction was given on PD, treatment of early symptoms, advancing disease and the development of motor response fluctuations and dyskinesia, and on the concept of continuous dopaminergic stimulation as an important basis of advanced therapies, with the focus on apomorphine infusion in particular. The general introduction ends with the thesis aim and outline.

Chapter two and chapter three report real-world data on the use of apomorphine in two cohorts of PD patients; one large cohort of patients treated in the University Medical Center Groningen and another cohort consisting of advanced PD patients with cognitive dysfunction, treated at the Rehabilitation Unit of the Groningen Parkinson’s disease Expertise Center (GPEC).

The aim of our retrospective analysis as described in chapter two, was to provide long-term data on motor and non-motor symptoms in a large cohort of 125 PD patients. As
expected, apomorphine improved motor response fluctuations and – to a lesser extent – dyskinesia, also on the longer term. Further exploration revealed that the degree of levodopa-equivalent daily dose (LEDD) reduction was an important factor, whereas the patients with the highest reduction in LEDD showed the best results. With regard to the non-motor symptoms, almost half of the patients had a history of visual hallucinations and 30% had even active hallucinations at the start of apomorphine treatment, which did not worsen after the start of apomorphine infusion, and even improved in some patients. The initiation of apomorphine was accompanied by a reduction of oral/transdermal dopamine agonists, and an increase of cholinesterase inhibitors and/or clozapine. This overall approach resulted in an improvement of existing visual hallucinations in most of the patients. Also night-time problems improved in most patients. Despite the good efficacy of apomorphine, 75% of the patients discontinued within four years, due to a perceived decrease of therapeutic effect in 63%. The perceived subjective decrease of effect might be related to an overly conservative dosing of apomorphine or to the development of dopa-resistant symptoms, such as freezing or dysphagia.

Chapter three described data of a cohort of elderly PD patients with moderate to severe cognitive dysfunction, including visual hallucinations, and orthostatic hypotension. Although initiation of apomorphine in this patient group is generally not recommended, because most studies have only included non-demented patients, apomorphine was well-tolerated if combined with proper identification and treatment of pre-existing cognitive dysfunction, visual hallucinations, or orthostatic hypotension, according to the current guidelines. In line with previous studies, subcutaneous infusion of apomorphine had a beneficial effect on motor response fluctuations, but there was no reduction in time with dyskinesia. A relatively too low apomorphine dose is the most likely explanation for this finding. Also in late-stage PD, especially in patients with visual hallucinations, dopaminergic medication is often reduced in order to overcome troublesome side-effects. All included patients received their treatment in our PD rehabilitation unit for 6-8 weeks. Thereafter, most patients could be discharged to their homes again. Apomorphine infusion was able to postpone definite nurse home admissions in most of these advanced PD cases.

Parkinson’s disease, apomorphine and visual hallucinations

The relationship between apomorphine and visual hallucinations in patients with PD is controversial. Contrary to common perception that dopamine agonists worsen neuropsychiatric symptoms, apomorphine can be well tolerated by patients experiencing visual hallucinations, as illustrated in chapter two and chapter three. There is some evidence that apomorphine has the potential to improve symptoms of visual hallucinations. The aim of chapter four was to review the underlying pathogenesis of visual hallucinations in PD, together with the impact of dopamine agonists in general and apomorphine in particular.
The current concept is that visual hallucinations arise from impaired bottom-up and/or top-down visual processing, which can be linked to cholinergic deficits and mono-amine imbalance, especially related to dopamine and serotonin. A key role in visual processing and the genesis of visual hallucinations is attributed to D₁-like dopamine receptors and the 5-HT₂A serotonin receptor subtype. Especially the 5-HT₂A receptor seems to be very relevant, as clozapine and pimavanserin, both known for their anti-hallucinogenic effect, predominantly act as 5-HT₂A antagonists. In contrast to other dopamine agonists, apomorphine possesses an agonist activity at D₁-like receptors and has an antagonistic activity at 5-HT₂A receptors, while all other dopamine agonists have an agonistic activity at this receptor. The unique receptor profile of apomorphine may be related to its chemical structure, containing a piperidine moiety, which is also part of several antipsychotics, like haloperidol and risperidone. The limited available data suggests that apomorphine has a relatively low tendency to induce – or even a beneficial effect on – visual hallucinations, which is in clear contrast to the other dopamine agonists, very likely based on the different and unique receptor profile of apomorphine.

**Apomorphine and skin reactions**

Subcutaneous nodules at the site of infusion are a common and troublesome side-effect of apomorphine. The pathogenesis of subcutaneous nodules is not completely understood and therefore the management of these nodules lacks proper evidence. But also other skin reactions are observed, as illustrated in chapter five.

In chapter five, two PD patients presented with a maculopapular exanthema on the trunk and extremities at day 13 and 14 after being started with CSAI. Prick and patch tests were performed to investigate an immediate or delayed hypersensitivity reaction, respectively. In both patients patch testing showed positive patch test reactions to sodium metabisulfite, an additive to the apomorphine solution. One of these patients also showed a positive reaction to the apomorphine solution for infusion, including sodium metabisulfite. Prick tests gave negative results. This suggests that the cutaneous drug reactions are presumably caused by a systemic delayed hypersensitivity reaction to sodium metabisulfite. Because of the severity of this reaction, one patient had to stop apomorphine, while in the other patient the rash resolved spontaneously within a few weeks, possibly related to hyposensitization.

Chapter six provided clinical evidence for the management of apomorphine-induced subcutaneous nodules. In a five-way fixed-sequence crossover trial, four frequently used treatment modalities, including massage with a spikey ball, topical hydrocortisone 1%, dilution of apomorphine 0.5% to 0.25% and subcutaneous hydrocortisone 10mg as pretreatment, were compared with no treatment. To elucidate the histopathology, skin biopsies were taken after each treatment modality. Ten patients completed all treatment arms. Our findings demonstrated that the most frequently used treatment
modalities, i.e. massage and topical hydrocortisone, had no added value, whereas dilution of apomorphine and pretreatment with subcutaneous hydrocortisone significantly improved subcutaneous nodule formation. Remarkably, no substantial changes in the histology of the subcutaneous nodules was seen after any of these treatments, which might be related to the formation of edema, which cannot be visualized in the biopsies.

**Chapter seven** reviewed the clinical and histological characteristics of apomorphine-induced subcutaneous nodules in PD patients, treated at the University Medical Center Groningen (UMCG), the Netherlands, combined with cases described in the literature. The histology of subcutaneous tissue showed a fairly consistent pattern. Biopsies of nodules with a maturation up to three days showed in most cases a panniculitis with varying amounts of eosinophils, together with histiocytes, lymphocytes and fat necrosis. After seven days most eosinophils disappeared, whereas no eosinophils could be identified after fourteen days. Instead of eosinophils, macrophages loaded with dark melanin-like pigment were visible in the Masson-Fontana staining after fourteen days of being treated with apomorphine. This melanin-like pigment is the end product of auto-oxidation of apomorphine, via the formation of ortho-quinones. However, these ortho-quinones cannot be visualized in the biopsies. The amount of pigment was inversely related to maturity of the nodules. Patients who had been treated for more than 6 months showed mainly fibrosis. The abundant presence of eosinophils points to the direction of a hypersensitivity reaction, rather than local irritation. However, allergic prick and patch tests did not confirm a hypersensitivity reaction. A likely explanation for the negative allergic work-up for apomorphine and sodium metabisulfite might be attributed to the concept of haptenation. In haptenation the molecule itself is not allergenic, but needs an attached protein to elicit a hypersensitivity reaction. A well-known example is urushiol, present in poison ivy, which rapidly undergoes auto-oxidation, creating ortho-quinones. As has been demonstrated in previous studies, patch tests with non-oxidized chemicals remain negative, while patients did react to the oxidized chemicals.

**General considerations and future perspectives**

This thesis presented *real-world data* on the use of apomorphine in two large cohorts of PD patients, focusing on the relationship between apomorphine and the occurrence of visual hallucinations and gave insight into the histopathology of apomorphine-induced subcutaneous nodules, in combination with an evidence-based approach for the management of these nodules. However, how should our findings be interpreted? In the next paragraphs our data will be discussed in a broader perspective.
Efficacy of apomorphine and long-term data on use of apomorphine infusion

Our retrospective follow-up study including 45 advanced PD patients (chapter three) showed that apomorphine infusion reduced OFF-time and increased ON-time significantly, whereas the duration of dyskinesia did not change, presumably due to underdosing, which is quite common in late-stage PD. Compared to the TOLEDO study, the reduction in OFF-time in our cohort was very similar (45% in our cohort versus 37% in TOLEDO), as well as the increase of ON-time (25% versus 33% in TOLEDO). Our data show that CSAI is still effective in treating motor response fluctuations in late-stage PD. This was already shown in multiple short-term, open-label studies and one randomized placebo-controlled trial – the TOLEDO study – however in much earlier stages of PD. The data on the reduction of dyskinesia with CSAI are inconsistent between several open-label studies. However, one small prospective study described a marked reduction in frequency and severity of dyskinesia in 12 PD patients after 6 months of CSAI treatment.

Apomorphine is usually well-tolerated and adverse events are mild to moderate. Skin reactions are the most common, followed by nausea and somnolence. Our real-world safety data from chapter three are in line with the previously described adverse event in observational studies and the TOLEDO study. However, the striking difference is that our cohort represented an older group of more advanced PD patients with cognitive deficits and visual hallucinations (up to 71% of the included patients). Overall visual hallucinations did not worsen, except from a few patients in whom the visual hallucinations progressed or started to occur during treatment with CSAI. Only in 3% of the patients these hallucinations led to discontinuation of CSAI. However, these results are the product of a combination of actions, being the infusion of apomorphine together with optimal treatment of the cognitive symptoms and visual hallucinations, which is therefore recommended for all advanced PD patients with an indication for continuous infusion therapy.

High drop-out of patients using apomorphine infusion

Apomorphine infusion showed a relatively high drop-out, as illustrated by the data from chapter two and three. During the first year of CSAI 25% dropped out, which increased to 50% after 3 years, and even up to >70% after 10 years. This drop-out rate is higher compared to the (retrospective) data from other advanced therapies like LCIG and Deep Brain Stimulation (DBS). LCIG infusion showed a drop-out rate in between 9.5 and 31% in the first year, while <5% stopped DBS of the subthalamic nucleus (DBS-STN) during the first year. The drop-out rate of LCIG on the longer term increases up to 45% after ten years, whereas 49% of patients discontinued DBS-STN during a 10 year follow-up.
However, the drop-out rate of apomorphine is rather comparable to other dopamine agonists, like ropinirole, pramipexole or rotigotine. Overall, after 3 years 51% patients had discontinued ropinirole, 60% pramipexole and 50% rotigotine.\textsuperscript{18,19}

Reasons for discontinuation of apomorphine was a lack of perceived efficacy (chapter two), whereas death was also an important reason, especially looking at the cohort from chapter three, with an high mean age of 70 years. For LCIG, the main reasons for discontinuation were death, device-related adverse events, especially within the first year, and also a lack of perceived effect.\textsuperscript{11-13,20-22} The main reason for discontinuation DBS-STN was death, partially due to suicide.\textsuperscript{14,15} Only a fraction of patients stopped treatment because of other reasons (0.9\% of patients requested to remove their electrodes) and in 0.3\% of patients the DBS was turned off due to lack of efficacy.\textsuperscript{15}

The advantages of CSAI treatment, being minimally invasive, not requiring surgery with a waiting list or extensive screening period, seems to be a disadvantage at the same time, looking at the adherence figures. Apparently, apomorphine infusion is also easy to stop. So, the adherence on apomorphine infusion actually should be compared to the oral/transdermal dopamine agonists.

Unfortunately, even 30 years after its introduction, apomorphine is still underutilized. One of the reasons may be the discontinuation rate over time, making it a last resort option. Thereabove, apomorphine is hardly ever prescribed as a monotherapy, which has popularized the use of LCIG. However, the ease of use and the results of the EARLYSTIM study may encourage offering CSAI at an earlier stage in the disease, to be considered if DBS-STN perhaps is a bridge too far, to increase quality of life in younger patients with motor fluctuations.\textsuperscript{23} In those cases the possibly shorter endurance of apomorphine infusion might be a less important drawback.

**Visual hallucinations and apomorphine infusion**

Contrary to common believes, apomorphine infusion was well-tolerated in PD patients with pre-existing visual hallucinations (see chapter two, three and four). The good tolerability of apomorphine is in clear contrast with other dopamine agonists.\textsuperscript{24} Part of this tolerance can be explained by the fact that oral/transdermal dopamine agonists could be reduced, and cholinesterase inhibitors and clozapine were provided, if considered appropriate. These findings are in line with previous reports.\textsuperscript{25,26} It was even hypothesized that apomorphine might have beneficial effects on existing visual hallucinations.\textsuperscript{26,27} The EUROINF open-label data showed improvement in perceptual and hallucination symptoms in patients treated with apomorphine infusion.\textsuperscript{28,29}

Apomorphine reduced hallucinations to a greater extent than LCIG, and to a similar extent as DBS, which might be attributed to a greater reduction in dopaminergic medication.\textsuperscript{29} These open-label data and clinical observations have to be considered
with caution, as patients with cognitive dysfunction are prone to develop a delirium with visual hallucinations, mostly related to other comorbid complications, such as infection.\(^\text{30}\)

Also the mode of administration, i.e. continuous infusion, avoiding peak-dose side effects, might have influenced the ultimate effect of apomorphine on visual hallucinations, when compared to other dopamine agonists.

Considering our data, there is an urgent need for a randomized prospective placebo-controlled trial to confirm the beneficial effects of (low-dose) continuous apomorphine infusion on visual hallucinations in PD.

**Cognition and infusion of apomorphine**

Up to 80% of PD patients develop PD dementia, although the course is variable, and stabilization of cognition – or even reversal to normal cognition – is not uncommon.\(^\text{31}\)

Clinical experience, supported by short-term data, suggests that apomorphine infusion seems to stabilize or even ameliorate cognitive functioning.\(^\text{32-36}\) In line with these observations, cognitive functioning in our cohort did not change after the start of apomorphine infusion (chapter three).

One of the explanations is the stimulation of D\(_1\)-like receptors in the frontal cortical regions by apomorphine, as can be depicted from the hypothesized Inverted U-shaped relationship between prefrontal functioning and dopaminergic activity (chapter four).

An interesting alternative explanation is related to the possible role of apomorphine in the deposition of amyloid in the brain. There is strong evidence that the extent of amyloid plaque formation is a significant contributor to dementia in up to one-third of patients with PD, whereas the role of tau-related pathology is less clear.\(^\text{31,37}\) Interestingly, apomorphine has shown in animal studies to reduce Aβ accumulation and toxicity, possibly via antioxidative mechanisms.\(^\text{38,39}\) In a recent postmortem study, PD patients without dementia who had received apomorphine treatment showed reduced Aβ deposition compared to untreated patients.\(^\text{40}\)

Whether these observations can be translated into a clinical therapeutic option for apomorphine, to improve cognitive impairment in Alzheimer’s disease or PD remains to be established via controlled clinical trials, in combination with PET-imaging of amyloid.

**Skin related problems due to subcutaneous infusion of apomorphine**

Skin-related problems are a real burden for patients, caregivers and treating physicians. In this thesis, two types of skin problems were presented. Firstly, two patients with a typical generalized rash after two weeks of apomorphine treatment. We demonstrated that this was based on a delayed hypersensitivity reaction to sodium metabisulfite –
an additive to the apomorphine solution. In recent years, an increasing number of PD patients has been reported with this type of rash after having started with apomorphine treatment. Over the last 25 years, the prevalence has increased from 1.4 to 7% in published case series. In addition, when the dosage of sodium metabisulfite will be doubled, as proposed by Hagell and colleague’s, we will face this adverse event more often in the upcoming years.

Secondly, the most common skin reaction is the development of subcutaneous nodules, occasionally associated with erythema. The underlying histopathological mechanism of subcutaneous nodules remains not fully understood, but we attempted to lump all the available evidence (chapter seven). It is hypothesized that breakdown products of apomorphine cause a delayed hypersensitivity reaction via the concept of haptenation. This hypothesis needs to be tested by performing patch tests including apomorphine ortho-quinones.

We demonstrated in a five-way, fixed-sequence crossover trial that dilution of apomorphine and pre-treatment with subcutaneous hydrocortisone (10 mg) improved subcutaneous nodule formation (chapter seven). Although PD nurses are always very positive about the effects of massage, this was not supported by our data, which was also true for the topical application of hydrocortisone 1%. Hopefully this will lead more frequently to diluting the apomorphine solution and to the application of 10 mg hydrocortisone subcutaneously and to the termination of topical hydrocortisone and massage, which is also a burden for the patients.

It might even be that diluted apomorphine (in this case 2.5mg/ml) will be the new standard, which can be diluted further on indication. However, lowering the apomorphine concentration results in less stable solutions. Apomorphine solutions of 1mg/ml with sodium metabisulfite (0.125%) retained their physiological activity and chemical stability for more than 6 months when kept below 4°C and shielded from air and light. However, concentrations that were lower than 1mg/ml were less stable. A solution of 0.05mg/ml was stable for less than 5 hours in 37°C. Looking at the influence of several antioxidants on the stability of an aqueous apomorphine solution, sodium metabisulfite (0.1%) had the worst stability profile. Even more remarkable is that apomorphine without any antioxidant was more stable than a formulation with sodium metabisulfite (0.1%), suggesting that sodium metabisulfite acts as inducer in specific circumstances. However, the combination of sodium metabisulfite (0.1%) with L-ascorbic acid (0.1%) as antioxidants, resulted in the most stable apomorphine solution. It is therefore recommended to add L-ascorbic acid (0.1%) to the current apomorphine formulation. Several other factors, such as pH, light and temperature, greatly influence the auto-oxidation of apomorphine in aqueous solutions, which needs further evaluation.

Pretreatment with subcutaneous hydrocortisone is sporadically used in clinical practice, but had the best outcomes with regards to subcutaneous nodule formation. A dosage of
10mg s.c. is comparable to 2.5 mg of oral prednisolone. On the short-term (months), no adverse events were seen, but there is lack of long-term data in this population.

In conclusion, apomorphine infusion is an underutilized and easy therapy for advanced PD patients with (motor) response fluctuations, with hardly strict contra-indications and a proven stable efficacy on the mid-long term. Prospective placebo-controlled trials should investigate its definite role in cognitively impaired PD patients with or without hallucinations.
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