Subcutaneous Apomorphine Infusion – An Update

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Abstract

Continuous delivery of dopaminergic drugs is an important treatment strategy to delay or reverse motor complications in Parkinson's disease (PD). Subcutaneous apomorphine (APO) infusion has been shown (in uncontrolled studies) to significantly reduce 'off' time and dyskinesia duration and severity, and long-term data show the beneficial effects persist for several years. There is some evidence that the maximum antidyskinetic effect of APO infusion may be attained when oral medications are reduced or discontinued, making monotherapy an important clinical goal. Recent studies demonstrate possible positive effects of APO infusion on the non-motor symptoms of PD. However, more trials are needed to assess the neuropsychiatric effects of this treatment. Moreover, randomised controlled trials are needed to compare APO infusion with best medical treatment and with other invasive treatments such as levodopa/carbidopa intestinal gel infusion and deep brain stimulation.

Keywords

Parkinson's disease, levodopa, continuous dopaminergic stimulation, subcutaneous apomorphine, non-motor symptoms

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The management of the later stages of Parkinson's disease (PD) is greatly impacted by non-dopaminergic problems, such as dementia, depression and falls, and by the emergence of motor complications including motor fluctuations and dyskinesias. Motor fluctuations, such as 'wearing off' and unpredictable 'off', affect 30–100 % of patients.[1–4] Dyskinesias can be 'on' (mostly choreatic), biphasic (often dystonic) or 'off' (dystonic). In the later stages of the disease, there is a loss of nigrostriatal neurons and a concomitant loss of storage capacity. Positron emission tomography imaging of dyskinetic and non-dyskinetic patients showed no difference in dopamine receptor binding, which suggests that dyskinesias are unlikely to be the effect of alterations in striatal dopamine receptor binding.[5] On the other hand, levodopa-induced changes in synaptic dopamine levels increase with the progression of PD.[6] These changes in synaptic dopamine concentration may be a factor in the emergence of peak-dose dyskinesias.

The pharmacokinetics of levodopa in the periphery, such as plasma half-life clearance, volume of distribution and maximum plasma concentrations, remain unchanged.[7] However, the absorption of oral levodopa, which takes place primarily in the duodenum, is affected as gastric emptying becomes more erratic.[8,9] Pharmacodynamic postsynaptic striatal changes in gene expression,[10] neuropeptide formation[11] and discharge patterns of the basal ganglia[12] result in complex feedback loops.[13] Furthermore, non-dopaminergic factors such as glutamate, opioids and serotonin may be involved in the development of dyskinesia.[14] Sprouting of extrasynaptic dopaminergic terminals may also lead to dysregulated dopamine release.[15]

One of the most important factors associated with the risk of motor complications is the degree of neuronal loss. In rats whose nigrostriatal system had been lesioned unilaterally by 6-hydroxydopamine, the level of levodopa-induced motor complications was related to lesion size.[16] In humans, if the first dose of levodopa is given at an advanced stage of the disease, motor complications may develop within a matter of weeks.[17] Furthermore, patients with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced chronic and severe parkinsonism developed dyskinesias or 'on-off' fluctuations within months of starting levodopa treatment.[14] Additional factors that contribute to a greater risk of motor complications include younger age at disease onset,[3,18] lower bodyweight[19,20] and genetic factors.[21]

In addition to neuronal loss, several factors relating to the treatment strategy are important in the development of motor complications. For example, the dose,[22] half-life and mode of delivery[23] of levodopa have a major impact on the emergence of motor complications. Clinical studies show that initial dopamine agonist treatment delays motor complications[24–27] and that the same drug (levodopa, apomorphine or lisuride) has different effects when administered continuously versus intermittently.[28–33] These findings led to the concept that pulsatile receptor stimulation leads to the development of motor complications, while continuous drug delivery can delay or reverse motor complications.

Table 1: Effect of Subcutaneous Apomorphine Infusion Treatment on Motor Symptoms, Non-motor Symptoms and Quality of Life as Assessed via Unified Parkinson's Disease Rating Scale (UPDRS), Non-Motor Symptoms Scale (NMSS) and Parkinson's Disease Questionnaire-8 (PDQ-8)

	Control			Apomorphine		
	Baseline	Follow-up	p	Baseline	Follow-up	p
UPDRS: motor exam	20.06 (9.68)	19.35 (12.80)	0.69	36.94 (11.42)	15.35 (8.21)	0.0003
UPDRS: complications	7.93 (5.43)	7.00 (4.46)	0.48	10.00 (6.43)	3.53 (3.52)	0.0003
NMSS:						
• Cardiovascular	1.29 (2.97)	1.18 (2.90)	0.45	4.65 (5.63)	2.76 (3.51)	0.03
• Sleep	12.29 (9.58)	12.06 (9.32)	0.90	22.06 (11.47)	10.71 (9.63)	0.0003
• Mood/apathy	8.35 (10.33)	8.06 (8.78)	0.79	22.76 (19.85)	11.29 (13.04)	0.0005
• Perceptual	2.23 (5.03)	2.59 (6.26)	0.90	4.59 (6.92)	1.88 (3.35)	0.04
• Attention	6.00 (8.40)	7.18 (7.76)	0.16	12.82 (9.62)	8.71 (7.75)	0.006
• Gastrointestinal	5.94 (5.97)	7.12 (6.49)	0.24	7.35 (7.35)	4.41 (5.11)	0.002
• Urinary	4.29 (3.57)	6.23 (4.26)	0.06	10.70 (8.93)	5.71 (6.72)	0.001
• Sexual	3.12 (6.58)	3.29 (6.12)	0.97	2.53 (5.96)	2.00 (3.94)	0.42
• Miscellany	4.12 (5.67)	4.29 (5.55)	0.61	18.47 (14.54)	9.47 (9.70)	0.0003
NMSS: total score	47.65 (43.40)	52.00 (37.65)	0.22	105.94 (65.43)	56.94 (45.39)	0.0003
PDQ-8	35.84 (23.10)	44.85 (17.57)	0.02	55.70 (19.80)	32.35 (21.54)	0.001

Baseline and follow-up figures are means with standard deviations in brackets. Benjamini-Hochberg correction: p<0.027. Source: Adapted from Journal of Parkinson's Disease, *1, P Martinez-Martin, P Reddy, A Antonini, T Henriksen, R Katzenschlager, P Odin, A Todorova, Y Naidu, S Tluk, C Chandiramani, A Martin and KR Chaudhuri, Chronic Subcutaneous Infusion Therapy with Apomorphine in Advanced Parkinson's Disease Compared to Conventional Therapy: A Real Life Study of Non Motor Effect, 197–203,[46] copyright © 2011, with permission from IOS Press.*

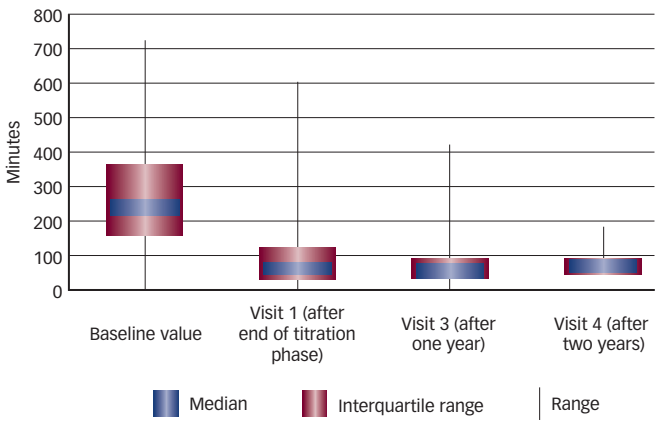
Effects of Apomorphine Infusion on Motor Symptoms of Parkison's Disease

Apomorphine is a potent dopamine agonist. When compared with levodopa, the two drugs result in a similar degree of improvement in motor function.[34] The advantage of apomorphine is its fast onset of effect (typically <10 minutes).[34] A randomised, double-blind, placebo-controlled study showed that a single injection of apomorphine greatly improved motor function, but may also induce dyskinesias.[35] Subcutaneous injection of apomorphine is indicated for rescue from refractory 'off', unpredictable 'off', 'off' dystonia and painful 'off'.

APO infusion treatment was developed to continuously deliver apomorphine. In the 1990s, this treatment was mainly used in addition to ongoing oral treatment for the relief of 'off' periods. Studies have shown 65 % reductions in 'off' periods with APO infusion and oral treatment combined.[36–38] Most did not report effects on dyskinesias, although one study described a decline in dyskinesia, with a corresponding reduction in levodopa dosage from 1,260 to 280 mg/dl.[39] However, longer-term studies showed that the discontinuation of oral treatment, to achieve monotherapy with APO infusion, led to greater improvements in dyskinesias.[31,32] In one study, patients were followed up for a mean of 33.8 months.[32] In both the monotherapy group and the polytherapy group, the duration of 'on' time increased (monotherapy group, 55 % to 83 %, p<0.005; polytherapy group, 53 % to 71 %, p=0.05). However, the mean maximum dyskinesia reduction was significantly higher in the monotherapy group than in the polytherapy group (64 % versus 30 %, p<0.001).

A small prospective study on the antidyskinetic effect of subcutaneous APO infusion used subjective and objective measures.[33] Twelve PD patients with 'on-off' fluctuations and disabling dyskinesias who were scheduled to start APO infusion treatment underwent acute levodopa and apomorphine challenges at baseline and six months later. After six months, the mean dose of apomorphine was 75.2 mg per day and the mean dose of levodopa had been reduced by 55 %. Daily 'off' time had decreased by 38 % (2.4 hours). In terms of dyskinesia, modified

Figure 1: Reduction in 'Off' Time After up to Two Years of Subcutaneous Apomorphine Infusion Therapy



Source: Adapted from F Sixel-Döring, H Klinke, K Hahn, G Ebersbach, P Odin, C Trenkwalder, Aktuelle neurologie, *Volume 38, Issue S 01, pp. S27–33,[44] copyright © 2011 Thieme. Reprinted by permission of Thieme.*

Abnormal Involuntary Movement Scale (AIMS) and Goetz scores were significantly reduced from baseline (both p<0.01). These findings were supported by patients' self-assessment scores on a visual analogue scale, items 32 and 33 of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Dyskinesia Subjective Rating Scale. Improvements in dyskinesia correlated with the decrease in oral medication and with the final apomorphine dose (p<0.05). Results from these and other uncontrolled studies suggest that it is beneficial to aim to reach monotherapy with APO infusion whenever possible, or at least to aim at the largest reduction possible in oral medication for each patient.

Long-term Data

Long-term follow-up studies have confirmed improvements in motor function with APO infusion therapy. For example, a two-year follow-up study showed a 61 % decrease in dyskinesias and a 47 % reduction in 'off' time,[40] and another study showed a 50 % reduction in dyskinesia at two years and a 29 % reduction at five years.[41]

Table 2: Changes in Non-Motor Symptoms Scale Items in the Subcutaneous Apomorphine Infusion Group

	Domains and Items	Baseline	Follow-up	p*
	Cardiovascular			
1	Light-headedness	3.53 ± 3.98	2.29 ± 3.06	0.03
2	Fainting	1.23 ± 2.63	0.47 ± 0.94	0.27
	Sleep/Fatigue			
3	Daytime sleeping	4.12 ± 4.44	2.88 ± 2.82	0.06
4	Fatigue	7.29 ± 3.93	2.82 ± 2.86	0.0004†
5	Difficulty falling asleep	5.12 ± 5.04	2.47 ± 3.22	0.008†
6	Restless legs	5.53 ± 4.02	2.53 ± 3.54	0.003†
	Mood/Cognition			
7	Lost interest in surroundings	2.94 ± 4.25	0.82 ± 2.13	0.009†
8	Lack motivation	3.65 ± 4.26	1.18 ± 1.74	0.009†
9	Nervous	6.12 ± 5.43	3.23 ± 3.47	0.003†
10	Sad	5.53 ± 4.98	2.88 ± 3.71	0.001†
11	Flat mood	2.23 ± 2.93	1.47 ± 2.87	0.09
12	Difficulty experiencing pleasure	2.76 ± 4.38	1.71 ± 3.22	0.015†
	Perceptual Problems			
13	Hallucinations	1.41 ± 2.45	0.53 ± 1.12	0.09
14	Delusions	1.53 ± 2.72	1.00 ± 1.87	0.3
15	Double vision	1.65 ± 3.26	0.35 ± 1.06	0.08
	Attention/Memory			
16	Problems with concentration	5.47 ± 4.49	3.29 ± 3.69	0.002†
17	Forget recent events	4.06 ± 3.53	2.88 ± 2.59	0.1
18	Forget doing things	3.29 ± 3.51	2.53 ± 2.65	0.2
	Gastrointestinal			
19	Dribbling saliva	2.23 ± 2.36	1.35 ± 1.97	0.015†
20	Swallowing	2.00 ± 2.52	1.00 ± 1.58	0.026
21	Constipation	3.12 ± 4.03	2.06 ± 3.44	0.026
	Urinary			
22	Urgency	3.71 ± 3.88	1.88 ± 2.87	0.005†
23	Frequency	2.59 ± 3.00	1.41 ± 3.32	0.015†
24	Nocturia	4.41 ± 3.78	2.41 ± 2.67	0.005†
	Sexual Function			
25	Altered interest in sex	1.59 ± 3.41	0.82 ± 1.74	0.05
26	Problems having sex	0.94 ± 3.01	1.18 ± 2.65	0.5
	Miscellaneous			
27	Unexplained pains	1.76 ± 3.99	2.59 ± 4.11	0.6
28	Lost taste/smell	4.41 ± 4.27	3.41 ± 4.18	0.05
29	Change in weight	3.00 ± 4.55	1.29 ± 2.23	0.05
30	Excessive sweating	7.59 ± 4.43	3.23 ± 3.77	0.001†

** Wilcoxon test; † Significant after Benjamini-Hochberg correction, p<0.025.*
Source: Adapted from Journal of Parkinson's Disease, *1, P Martinez-Martin, P Reddy, A Antonini, T Henriksen, R Katzenschlager, P Odin, A Todorova, Y Naidu, S Tluk, C Chandiramani, A Martin and KR Chaudhuri, Chronic Subcutaneous Infusion Therapy with Apomorphine in Advanced Parkinson's Disease Compared to Conventional Therapy: A Real Life Study of Non Motor Effect, 197–203,*[46] *copyright © 2011, with permission from IOS Press.*

Other studies found less improvement with APO infusion. For example, a non-randomised study compared APO infusion with deep brain stimulation (DBS) in advanced Parkinson's disease (APD) patients who fulfilled Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) criteria;[42] the mean treatment duration was 30 months and the grand mean APO infusion dose at the last visit was 83.4 mg per day, with a mean reduction in levodopa equivalent dose of 41 %; both APO infusion and DBS reduced daily 'off' time at one year and at last follow-up, but only DBS decreased dyskinesia duration and severity. The smaller amount of dyskinesia improvement with APO infusion shown in this study may partly be related to the degree of reduction in levodopa equivalent dose – an important consideration in interpreting results of this therapy.

A Spanish multicentre retrospective study showed that 83 of 166 patients remained on APO infusion therapy at four years.[43] The reasons for terminating treatment included: lack of support (nine patients), lack of effect (eight patients), adverse effects (18 patients) – including skin changes (four patients), psychosis (nine patients), cognitive worsening (four patients) and haemolytic anaemia (one patient) – other illnesses (11 patients), loss to follow-up (four patients), switch to DBS (13 patients) and switch to levodopa/carbidopa intestinal gel (LCIG) infusion (four patients). In patients who continued on APO infusion, the mean dose was 72 mg per day and the levodopa equivalent dose was reduced by 43 %. There was a marked reduction in 'off' duration (6.6 to 1.4 hours per day) and a 31 % reduction in dyskinesia severity.

Another multicentre study demonstrated that, at two years, 53 of 62 patients remained on APO infusion.[44] The reasons for terminating treatment were similar to the Spanish multicentre study:[43] adverse effects (eight patients), insufficient efficacy (four patients), death during the observation period (four patients), concomitant disease most likely not related to apomorphine (three patients), insufficiently treated medication-induced paranoid psychosis probably related to apomorphine (one patient) and loss to follow-up (six patients).[44] The mean apomorphine dose was 78 mg per day and the levodopa equivalent dose was reduced by 32 %. 'Off' time was reduced by 79 % (see *Figure 1*) and there was a subjective improvement in dyskinesia in 33 % of patients and no difference in 52 % of patients. The treatment was rated as 'good' by 76 % of the patients.

In a proof-of-concept study, six PD patients with severe subcutaneous nodule formation as a result of long-term subcutaneous APO infusion were switched to intravenous apomorphine via a long-term in-dwelling venous catheter.[45] Very stable plasma apomorphine levels and clinical functioning throughout the day were achieved.

The results of comparative and open-label studies on APO infusion are in keeping with the concept that switching from intermittent to continuous administration of apomorphine may underlie the improvement in motor complications. However, so far, there have been no randomised, controlled trials of this treatment.

Effects of Apomorphine Infusion on Non-motor Symptoms of Parkinson's Disease

A recent multicentre and comparative (but not randomised) study compared 17 PD patients on APO infusion and 17 patients eligible for apomorphine pump therapy who did not receive this treatment.[46] There were some differences between the APO and control groups at baseline: the control group had better scores in the UPDRS-III, the Non-Motor Symptoms Scale (NMSS) and Parkinson's Disease Questionnaire-8 (PDQ-8). At one year follow-up, levodopa equivalent dose was significantly reduced in the APO group (1,078 ± 446 to 459 ± 282 mg, p<0.0001) and a large effect size of intervention was noted. This improvement was not observed in the untreated group. Moreover, the APO group showed significant

improvements in UPDRS-III (p=0.0003), PDQ-8 (p=0.001) and NMSS total scores (p=0.0003) (see *Table 1*). In addition, APO infusion treatment was tolerated in patients with visual hallucinations, illusions and paranoid ideations, and resulted in significant improvements in specific non-motor symptoms (NMS) such as excessive sweating, nocturia, urgency of micturition and fatigue (see *Table 2*). The number needed to treat for improvement >1 standard error of the mean (SEM) in the APO infusion group was lower than 2 for UPDRS-III, NMSS and PDQ-8 total scores.

These results demonstrate the positive effects of APO infusion therapy on NMS, including a significant effect on mood/cognition (see *Table 2*). Other open-label, non-randomised studies had shown APO infusion therapy to have no effect on cognition.[42,47–49] In comparison, DBS either had no effect on cognition[49] or led to a worsening.[42,47,48] Some studies have demonstrated improvements in depression with APO infusion treatment[49,50] while others found no effect.[47,48] Randomised studies are needed to study the effects of this treatment on NMS, in particular on neuropsychiatric problems.

Adverse Effects of Subcutaneous Apomorphine Infusion Therapy

Adverse effects of subcutaneous APO infusion therapy include dopaminergic effects (such as nausea, orthostatic hypotension, sleepiness, leg oedema), impulse control disorders and dopamine dysregulation. Another adverse effect is haemolytic anaemia, which is rare (≤2 %).[51] Mild-to-moderate skin reactions in the form of nodules (aseptic panniculitis) are the most common side effect. These may lead to absorption problems, but complications such as ulcerations and abscesses are rare.

Conclusions

There are now several treatment options for switching from intermittent to continuous dopaminergic stimulation (CDS) therapy. Great improvements in motor and non-motor functioning can be achieved with CDS therapy, but limitations remain.

Dopaminergic stimulation is tonic under physiological conditions, but dopamine levels are not completely constant. In addition, little is known about how dopaminergic drugs stimulate the receptors.[52]

Importantly, none of the available treatments influence the progression of the disease, which still leads to increased mortality and a considerable burden of disability. A follow-up study showed that among those patients who were still alive 20 years after PD diagnosis, 48 % were in a nursing home, 83 % had dementia, falls occurred in 87 % of them and incontinence in 71 %.[53] The real goal of research efforts is, therefore, to stop or reverse the progression of PD, but in the meantime continuous drug delivery remains an important clinical goal in an effort to reverse motor complications.

In order to achieve the full antidyskinetic potential of APO infusion, it is important to reduce oral medications and attain monotherapy or near-monotherapy whenever possible. Many questions remain unanswered with APO pump treatment, such as its neuropsychiatric effects and the best time to start treatment. Moreover, randomised controlled trials are needed to compare subcutaneous APO infusion with best medical treatment and with LCIG infusion and DBS. More longer-term data on APO infusion are emerging, and the available data strongly suggest that CDS therapies such as APO infusion have an important role and are likely currently underused. ■

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