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Chronic Subcutaneous Infusion Therapy with Apomorphine in Advanced Parkinson's Disease Compared to Conventional Therapy: A Real Life Study of Non Motor Effect

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Abstract. *Background*: Apomorphine infusion therapy remains under-used and there are no comparative studies of motor and non-motor effects of apomorphine infusion.

Methods: In this paper we report preliminary results from an ongoing clinical observational "real life" surveillance-based study focused on effects of this therapy on non-motor symptoms and health-related quality of life in a group of patients on apomorphine.

Results: Apomorphine infusion led to highly significant improvements in UPDRS 3 ($p = 0.0003$), UPDRS 4 ($p = 0.0003$), PDQ-8 (Parkinson's disease questionnaire, $p = 0.001$) and NMSS total (non motor symptoms scale, $p = 0.0003$). Furthermore, apomorphine was tolerated in patients with visual hallucinations, illusions and paranoid ideations while significant improvement in specific non-motor symptoms such as hyperhidrosis, nocturia, urgency of micturition, and fatigue was recorded. Levodopa equivalent dose decreased significantly (1077.81 ± 446.26 to 458.75 ± 282.29, $p < 0.0001$) and a large effect size of intervention was noted. In an untreated group no such improvement was noted. The number needed to treat (NNT) for improvement >1 SEM in the Apo group was calculated and was lower than 2 for >1 SEM improvement of UPDRS 3, NMSS, and PDQ-8 total scores.

Conclusions: This pilot observational study suggests that non-motor effects are evident with apomorphine therapy and patients suitable for apomorphine deteriorate in the absence of therapy.

INTRODUCTION

Subcutaneous administration of apomorphine (Apo) has been used as treatment for advanced Parkinson's disease (PD) with refractory on-off periods and dyskinesias and is nationally recommended in many

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countries [1–10]. We have reported the beneficial effect of apomorphine infusion on aspects of non-motor symptoms (NMS) of PD as assessed by the validated PD NMS scale (NMSS) [11–14]. There are no studies comparing non-motor effects of apomorphine infusion in two groups of PD patients deemed suitable for apomorphine therapy yet where one group is treated by conventional (oral and patch therapy) treatment only because of local funding issues.

PATIENTS AND METHODS

Between 2008–2009, 17 PD patients (all satisfying the UK PD brain Bank criteria) [15] with severe dyskinesias (as rated by patients, carers and clinician) and on-off fluctuations unresponsive to changes in existing therapy were started on apomorphine infusion (12–16 hrs/day) and followed up in centres across Europe. All had baseline assessment ("7 to 10 days pre-treatment" of motor function (Unified Parkinson's Disease Rating Scale, UPDRS 3 and 4) [16], Hoehn and Yahr staging (HY) [17], Non-Motor Symptoms Scale (NMSS) [13, 14] and health-related quality of life (HRQoL) (Parkinson's disease questionnaire, PDQ-8) [18]. Follow-up assessments were carried out in a manner similar to that recently reported [8]. For analysis, baseline data was compared to the last available follow-up visit of each patient at "on" stage.

Seventeen PD patients were selected for comparison (C) as these patients were not funded for apomorphine. These patients also had severe dyskinesias and on-off fluctuations unresponsive to further modifications in their existing therapy. These patients were followed up while on best conventional therapy using the same clinical protocol. As this was a clinically dictated study, matching for C and Apo cases from individual centres was not possible.

As this was a clinical observational surveillance audit based study, with a licensed drug for the approved indication specific ethical approval was not required, as confirmed by written statements from the Bispebjerg Hospital, Copenhagen ethics committee and ethics committee in Donauspital, Vienna. Use of NMSS methodology was approved for use by the ethics committee of the University Hospital of Lewisham, Kings College Hospital, Madrid, and Bremerhaven.

Statistical analysis

Chi-squared and Fisher's exact tests were used for comparison of proportions, while non-parametric tests were applied for ordinal and continuous variables. Multiple comparisons were corrected by the Benjamini-Hochberg method [19] and for the association of changes Spearman rank correlation coefficient was used [20]. For each measure, the relative change [RC = mean $(\text{test}_{T2} - \text{test}_{T1}) \times 100/\text{mean test}_{T1}$)], the effect size [ES = mean $(\text{test}_{T2} - \text{test}_{T1})/\text{SD test}_{T1}$] and the standardized response mean [SRM = mean $(\text{test}_{T2} - \text{test}_{T1})/\text{SD}(\text{test}_{T2} - \text{test}_{T1})$] were calculated to determine the magnitude of change. For both effect size indices, ES and SRM, the standard values are: 0.20–0.49, Small effect; 0.50–0.79, Moderate effect; and $\geq$0.80, Large effect [21–23]. The number needed to treat (NNT) for improvement >1 SEM in the Apo group was calculated [24–27].

RESULTS

Seventeen Apo (mean age 59.5 ± 11.7 yrs, disease duration 12.05 ± 4 yrs, median HY score 4) were started on apomorphine infusion using a standardised local initiation protocol and the data compared to 17 C patients (mean age 66.4 ± 7.0 yrs, disease duration 13.23 ± 4.7 yrs, median HY score 3.9) over a period of 12.5 ± 11.5months. At baseline, there were no significant differences between Apo and C with respect to age, gender and PD duration and both groups were on comparable levodopa and dopamine agonist treatments and had resistant on-off fluctuations and dyskinesias. The levodopa equivalent (LDE) doses in both groups were similar between Apo (1077.81 ± 446.26 mg) and C (1028.18 ± 388.76 mg) at baseline. At baseline, the UPDRS 3, NMSS-Total and PDQ-8 showed significant differences between C and Apo group, the C group being lower in scores (indicative of better state). During follow-up, the C group showed worsening in PDQ-8 (Table 1) while Apo showed highly significant improvements in UPDRS 3 ($p = 0.0003$), UPDRS 4 ($p = 0.0003$) PDQ-8 ($p = 0.001$) and NMSS total ($p = 0.0003$, Table 2). The LDE increased significantly during follow-up in the C group (1028.18 ± 388.76 to 1154.54 ± 407.09 mg, $p = 0.001$) while in the Apo, LDE decreased significantly (1077.81 ± 446.26 to 458.75 ± 282.29, $p < 0.0001$) with improvement affecting more than 90% of patients and large effect size. In the Apo group, moderate to large effect size on the NMSS domains of sleep, mood/apathy, attention, gastrointestinal, urinary, sexual, and miscellany was evident (Table 3).

In the Apo group, there was a high correlation between change in UPDRS 3 and PDQ-8 ($r_s = 0.85$) and moderate between change in NMSS and PDQ-8

Table 1
Changes following Apomorphine infusion and continuing conventional therapy (comparator) in motor, non-motor, and quality of life dimensions

	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

Benjamini-Hochberg correction: $p < 0.027$; UPDRS: Unified Parkinson's Disease Rating Scale; NMSS: Non-Motor Symptoms Scale; PDQ-8: Parkinson's Disease Questionnaire-8 items.

($r_s = 0.44$). The NNT was lower than 2 for >1 SEM improvement of UPDRS 3, NMSS, and PDQ-8 total scores. The average NNT for NMSS domains was 3.95 (Table 4).

DISCUSSION

Our key observations from this study are as follows:

1. There was a large beneficial effect of apomorphine infusion on the whole of NMSS observed along over one year average follow-up (Tables 2 and 3).
2. Patients with visual hallucinations, illusions and paranoid ideations reported no worsening after apomorphine infusion.
3. Apomorphine infusion resulted in significant improvement in some specific NMS such as hyperhidrosis, nocturia, urgency of micturition, and fatigue.

Our "real life" study included patients who may be excluded in randomised clinical trials and so we used a pragmatic post-treatment surveillance method. The follow-up period is therefore variable as clinical appointments were based on the discretion of the clinicians or local arrangement methods as also reported

Table 2
Change in the items of Non-Motor Symptoms Scale (Apomorphine infusion group)

	Items & Domains	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	Difficult 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 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	Difficult 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

Table 2
(*Continued*)

	Items & Domains	Baseline	Follow-up	*p**
	Cardiovascular			
	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, $p < 0.025$.

from a large multicentre study of apomorphine infusion [8].

Apomorphine demonstrated benefit with a moderate to large effect size in all domains of NMSS (Table 3) along with UPDRS and PDQ-8. These data for the first time indicate efficacy of apomorphine infusion on NMS and improvement in HRQoL similar to the effect of intra-jejunal levodopa gel infusion in advanced PD as shown in a previous report from our group [28]. The NNT confirmed a beneficial effect for most patients, both for motor and non-motor manifestations (Table 4).

We also report non-worsening of the perceptual and attention domain of NMSS (Tables 2 and 3) following apomorphine, contrary to what is to be expected with the use of a potent dopamine agonist in advanced PD. Apomorphine may have a psychotropic action based on its constituent anti-psychotic piperidine moiety [2, 3, 7, 29]. Improvement of psychosis was reported in 1978 in a placebo controlled study of apomorphine in 18 chronic schizophrenic patients [30]. In PD, open label

Table 3
Effect of the intervention (Apomorphine infusion grup) in relation to motor, non motor and quality of life measures

	% of patients			Δ FU–B	Relative	Effect	Standardized
	I	NC	W		change	Size	Response Mean
UPDRS-Motor exam	100	0	0	–21.6 (9.56)	–58.44	1.89	2.26
UPDRS-Complications	94	6	0	–6.47 (4.91)	–64.70	1.01	1.32
NMSS-Cardiovascular	29	71	0	–1.88 (3.71)	–40.86	0.33	0.51
Sleep	100	0	0	–11.35 (6.93)	–51.45	0.99	1.64
Mood/apathy	82	18	0	–11.47 (10.90)	–50.39	0.58	1.05
Perceptual	41	53	6	–2.71 (5.19)	–59.04	0.39	0.52
Attention	71	23	6	–4.12 (7.31)	–32.14	0.43	0.56
Gastrointestinal	59	41	0	–2.94 (3.77)	–40.00	0.40	0.78
Urinary	71	29	0	–5.00 (5.26)	–46.70	0.56	0.95
Sexual	82	6	12	–0.53 (2.50)	–20.95	0.78	1.12
Miscellany	94	6	0	–9.00 (10.80)	–48.73	0.62	0.83
NMSS-Total score	100	0	0	–49.00 (36.62)	–46.25	0.75	1.34
PDQ-8	94	0	6	–23.34 (17.75)	–41.92	1.18	1.31

UPDRS: Unified Parkinson's Disease Rating Scale.
NMSS: Non-Motor Symptoms Scale; PDQ-8: Parkinson's Disease Questionnaire-8 items; I: Improved; NC: No changed; W: Worsened; Δ FU–B: Difference follow-up – baseline; mean (SD); For Effect size and Standardized Response Mean: 0.20–0.49, "small" effect; 0.50–0.79, "moderate" effect; and ≥0.80, "large" effect.

Table 4
NNT in patients treated with Apomorphine

	SEM	% of patients improving >1 SEM	NNT
UPDRS-Motor exam	10.48	82.35	1.21
UPDRS-Complications	5.34	47.06	2.12
NMSS- Cardiovascular	3.33	23.53	4.25
Sleep	8.11	58.52	1.71
Mood/apathy	11.74	41.18	2.43
Perceptual	4.89	17.65	5.67
Attention	6.08	29.41	3.40
Gastrointestinal	3.68	29.41	3.40
Urinary	5.21	35.29	2.83
Sexual	2.06	11.76	8.50
Miscellany	10.28	29.41	3.40
NMSS-Total score	42.40	52.94	1.90
PDQ-8	15.46	70.60	1.42

NNT = (1/% Improved) × 100; (n = 17).

studies had suggested safety of apomorphine infusion in those with neuropsychiatric problems on oral therapy [29, 31]. Tolerability of apomorphine infusion in our study may also be partly due to a significant reduction in LDE and cessation of therapy with other oral dopamine agonists, except the use of rotigotine patch in some cases.

The NMSS has been validated in over 600 patients and allows assessment of specific NMS within one instrument [13, 14]. Using NMSS, we report significant beneficial effects on sleep disturbances such as onset insomnia and restless legs while excessive daytime sleepiness was not worsened. Other NMS effects included a significant improvement in fatigue, motivation, anxiety, flat mood, anhedonia, attention deficit, dribbling of saliva, urinary dysfunction, particularly urgency and nocturia, and hyperhidrosis (Table 2). Some of these NMS may have an underlying dopaminergic basis while in others the improvements indicate successful amelioration of subtypes of non-motor off periods [32]. Our data also supports data from previous open-label studies reporting a beneficial effect of apomorphine infusion on sleep (notably severe insomnia), anhedonia and night time pain and cramps suggestive of restless legs syndrome [11, 12, 29, 33].

This is not a randomised controlled study and we do not have a true control group. However, data from randomised controlled trials may occasionally have limited external validity [34]. We studied small number of patients although by comparison, the only other comparative study addressing apomorphine and deep brain stimulation included 13/12 patients only [35]. Similarly, the only comparative study of apomorphine versus levodopa infusion included 4 patients only [36]. In our study, a moderate to large effect of apomorphine was evident with the current sample size.

In conclusion, this observational post-treatment surveillance based study indicates the non-motor effects of apomorphine infusion. Specific non-motor effects of apomorphine are highlighted, calling for controlled studies with non-motor primary endpoints.

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