Original Article

Apomorphine: The Initial Indian Experience in Relation to Response Tests and Pumps

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Abstract

Background: Apomorphine is an option for continuous dopaminergic therapy in Parkinson's disease (PD). However, its effects in varied populations are limited due to its availability. **Objective:** To assess the efficacy and outcomes of apomorphine in Indian patients. **Materials and Methods:** Retrospective analysis of PD patients who underwent apomorphine response test (ART), along with the subset, who went on to apomorphine pumps. **Results:** Twenty-nine confirmed PD patients underwent ART and all PD patients showed good clinical response. 19 subjects developed adverse events which included: nausea (*n*-15, 51.7%), vomiting (*n*-10, 34.4%), sleepiness (*n*-08; 27.5%), yawning (*n*-07, 24.1%), postural hypotension (*n*-03, 10.3%), dizziness (*n*-03, 10.3%), and profuse sweating (*n*-01, 3.4%). Apomorphine pumps were initiated in six subjects, with significant clinical improvement. Adverse events on pump included subcutaneous nodules, nausea, hypersexuality. Two among them subsequently discontinued the pump primarily due to financial constraints. **Conclusions:** Apomorphine adds up to the armamentarium for treatment of PD patients in India with good clinical responses.

Keywords: Adverse effects, apomorphine pumps, apomorphine response test, India

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder wherein there is a progressive loss of neurons especially in substantia nigra, leading a plethora of clinical symptoms (motor and non-motor) among which rigidity, bradykinesia, and tremors predominate. Unlike most of the neurodegenerative disorders, PD has good symptomatic treatments which improve the quality of life significantly. Among varied treatments, levodopa remains the central anchor in management of PD. However, over the time, the pulsatile therapy with levodopa has its own limitations leading to varied motor fluctuations. Currently, during this phase, the option is to move from pulsatile dopaminergic therapy to continuous dopaminergic therapy. The current available options for continuous dopaminergic therapy include deep brain stimulation (DBS), apomorphine pumps, dopamine agonist patches, and levodopa pumps.[1] Until now, among these options, only DBS was available in India. Albeit apomorphine is available in global market for more than a quarter of century, it has only been launched in India this year (2019). The factors for this could have been multifold, including that of cost, feasibility, etc. Apomorphine is a potent non-ergot derived dopamine agonist, which has a history longer than that of levodopa. However, its regular clinical utilization in PD is noted during last 3 decades only [Figure 1].[2,3] Apomorphine is derived from morphine, by a process wherein its all narcotic and opiate effects are eliminated (hence no opiate/direct pain reliving properties).[4] This derived molecule from morphine contains a moiety, in homologous to dopamine molecule, explaining its benefits for PD.[5] It is used for clinical assessment of dopaminergic response in Parkinsonism subjects and for management of moderately advanced PD either as rescue therapy or as an continuous dopaminergic stimulation therapy using a pen or a pump, respectively.[3] In this study, we present our initial experiences in using apomorphine during the apomorphine response test (ART) and utilization of apomorphine pumps.

Materials and Methods

The study involved the retrospective analysis of subjects who underwent ART at the Institute between March 2019 and June 2019. The study was approved by the Institute Ethics Committee. All subjects were assessed by neurologists and included both clinically confirmed PD patients according to Queens Square Brain Bank Criteria (except for patients with more than one first degree affected relative were allowed).[6] The inclusion criteria for ART in PD patients was clinically confirmed PD subjects with significant levodopa-related

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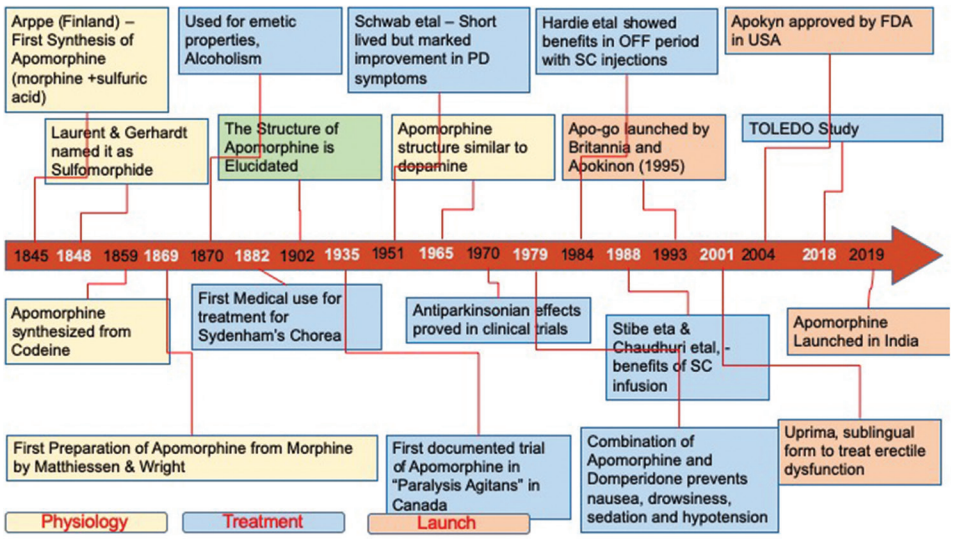

Figure 1: Timeline of various critical events in relation to invention and critical clinical events of apomorphine.[2,4]

therapies and in clinically OFF state. Figure 2 shows the flow chart protocol of the ART conducted. Apomorphine dosages were escalated until good clinical benefits were recorded, or subjects developed clinical adverse effects. Clinical data in relation to their demographic and disease profile, effects or adverse effects in response to apomorphine were collected. Subjects who met inclusion criteria for apomorphine pump (clinically confirmed PD, significant levodopa related motor fluctuations not optimized by medical treatment, good benefit with apomorphine response test) and among them who were willing to initiate on the pump were included in this analysis.

Results

Apomorphine Response Test

Twenty-nine patients (M:F – 19:10) underwent apomorphine response test, with a mean age of 60.45 ± 11.22 (range: 37-81 years). The mean duration of PD symptoms was - 120.79 ± 70.57 months (range: 36--276 months) and baseline OFF UPDRS score of 47.44 ± 19.85 (range: 19--93.5). All subjects were pretreated with domperidone either for 3 days or on the day of testing. Their clinical responses to ART are shown in Figure 3. The maximum dosage tried was 7 mg. One subject with primarily non-levodopa responsive symptoms due to disease progression appeared to have worsening of gait with ART. It was also noted that the clinical benefits were getting pleatued or mild worsening in other subjects, following development of adverse effects. This could be attributed to possibly reduced effort following the adverse effects.

Among 29 subjects, 19 (65.5%) (M: F-13:6) developed adverse effects. The most common adverse effect was nausea (*n*-15, 51.7%), vomiting (*n*-10, 34.4%), sleepiness (*n*-08; 27.5%), yawning (*n*-07, 24.1%) [Video Segment 1], postural hypotension (*n*-03, 10.3%), dizziness (*n*-03, 10.3%), and profuse sweating (*n*-01, 3.4%). The dosages at which adverse effects noted varies with following frequencies:

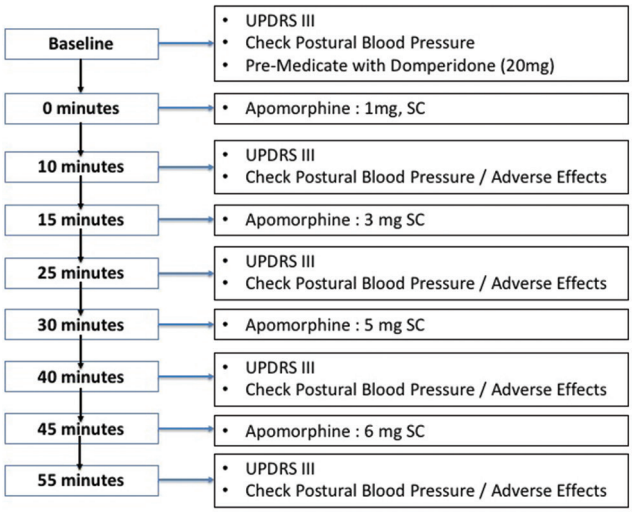

Figure 2: The flow chart of apomorphine response test protocol

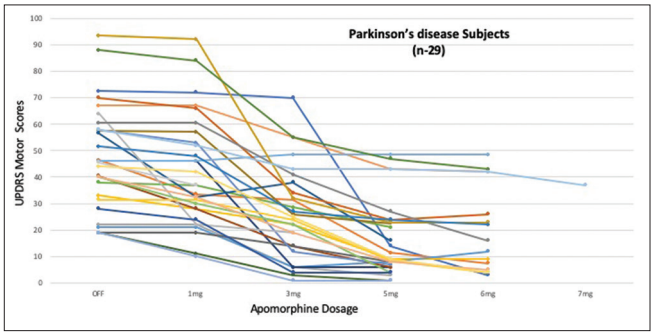

Figure 3: The clinical response in relation to apomorphine in Parkinson's disease subjects and other Parkinsonian syndrome for various dosages in relation to unified Parkinson's disease Rating Scale–Motor Section (UPDRS III)

motor fluctuations. All assessments for ART were initiated after at least 12--14 h of OFF from levodopa/dopaminergic

Table 1: Apomorphine pump subjects profile

Subject	Current Age	Duration of Symptoms (months)	LEDD[a] before Apomorphine pump	Current Apomorphine dosage	Current Standalone levodopa dose	Any adverse events	Total duration of pump utilization
1	50	84	2,000 mg	7.5 mg/h	300 mg	Nodules, Nausea	10 weeks
2	41	120	660 mg	3 mg/h	150 mg	Nodule, Hypersexuality	8 weeks
3	51	132	718.5 mg	4 mg/h	Baseline	None	1-2 weeks[b]
4	54	144	648 mg	4.5 mg/h	Baseline	?Sleep issues	4 weeks[c]
5	64	230	986	3.5 mg/h	150 mg	Nodules	9 weeks
6	66	84	1100	5 mg/h	200 mg	Nodules	8 weeks

[a]Tomlinson *et al*.[16]. [b]Discontinued after one week due to finances. Using Apomorphine as rescue therapy. [c]Discontinued after 4 weeks. Details not informed. Sleep issues/? Financial issues

1 mg (*n*-2), 3 mg (*n*-11), 5 mg (*n*-12), 6 mg (*n*-3). In one subject, the ART was abandoned due to severe postural hypotension at 1 mg of apomorphine. Another subject went on to sudden deep sleep after receiving 6 mg of apomorphine [Video Segment 2]. Subjects did develop dyskinesia with apomorphine, but were not considered in adverse effects profile [Video Segment 3].

All the subjects were pretreated with domperidone 20 mg prior to test. Among the subjects who underwent ART, most were treated for at least 3 days prior to ART vs another cohort which took it only on the day of testing. A sub-analysis to see the requirement of 3 days pretreatment vs "on spot" pretreatment with domperidone showed no significant difference between these two subsets ($P = 0.693$).

Apomorphine pump experience

Six out of 21 PD subjects who underwent ART for clinical indications went on to apomorphine pump with good clinical improvements and significant reduction in levodopa dosages and OFF periods [Table 1]. Two subjects discontinued treatment after 2 weeks and 1-month duration, respectively, due to financial limitations. Subcutaneous nodules were noted in all the subjects [Figure 4]. However, these were non-severe and would disappear over 48--72 h. Skin hygiene and rotation of injection sites had helped to reduce any complications in relation to the subcutaneous nodules. Two patients noted nausea and was managed with domperidone tablets. One subject was noted to have hypersexuality following the pump. However, according to the spouse, the features were present when levodopa was initiated initially; however, over the course, the effects had reduced. These symptoms have flared up following initiation of apomorphine and overall improvement in quality of life and ON periods. The main limitation noted was that of suboptimal utilization of pumps to reduce the cost burden. The apomorphine is supplied in ampoules of 50 mg each and those patients who require more than 50 mg/day were noted to compromise the dosage either by reducing the flow dosage rate or duration of pump utilization.

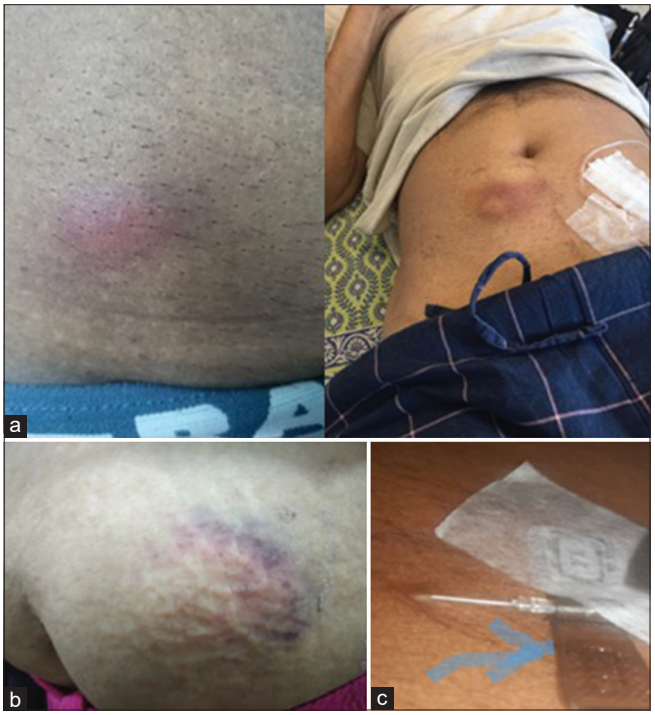

Figure 4: Clinical adverse events noted in relation to utilization of apomorphine pumps. (a) subcutaneous nodules; (b) purpuric patches at the injection site; (c) improper application of the insertion needle

Discussion

Apomorphine is a highly potent dopamine agonist which is used for various experimental and therapeutic indications since its initial synthesis in 1845.[2] Almost for a century since its discovery, its utilization was limited for its emetic properties (aversive conditioning in alcohol dependence, gastric emptying in poisoning and in respiratory disorders). Subsequently, it has been used as a hypnotic/sedative, sexual dysfunctions (erectile dysfunction), and various movement disorders including PD, restlessness leg syndrome, muscle spasms, tardive dyskineisa, tic disorders, and chorea.[2] Even though apomorphine was first tried for PD in 1884 by Dr. Edmond Weill, it had taken a back seat due to its emetic properties and poor availability through gastrointestinal system. It started to come into mainstream treatment of PD once it was shown that its emetic properties could be well controlled with domperidone/haloperidol/metoclorpramide.[7,8] Since 1990, with inception of pump technology, apomorphine has become one of the options

for continuous dopaminergic therapy. Apomorphine is currently available in injectable formulas only due to its limited GI absorption. This perse has created a boon for apomorphine, which bypasses the GI phase leading to quick absorption (~5.8 mins) with peak clinical benefits within 4–10 min of subcutaneous injections. It has a peak plasma concentration around 10--20 min of injections with clinical response lasting for 45--60 min.[2,4,9,10] These pharmacological properties have become the biggest strength of apomorphine, wherein it avoids the gastric motility related issues during the later phase of PD. It also has its own set of adverse effects due to its mode of administration and pharmacological features, which include skin nodules, erythema, hallucinations, headache, somnolence, hypotension, nausea, vomiting, coombs positive anemia.[11-13] Due to its quick and predictable responses, it helps as rescue therapies for PD subjects where in dosage failures and delayed ON is noted in relation to oral levodopa. Based on above benefits, currently apomorphine intermittent injections are suggested for subjects with: (1) severe OFF periods, (2) sudden OFF's, (3) delayed ON, and (4) morning akinesia. The apomorphine pumps are suggested for subjects who: (1) require too frequent rescue injections, (2) significant peak dose dyskinesia, (3) bothersome non-motor symptoms in OFF periods, (4) gastric absorption related issues, (5) surgical contraindicated for DBS due to other medical issues, and (6) people who are averse to the idea of surgical option for continuous dopaminergic stimulation therapy.[3,14,15]

Unlike levodopa, even after about 30 years since apomorphine utilization in regular management of PD, its availability across the globe is very limited. Hence, there is paucity of apomorphine data in various population groups. This study provides outcomes of initial apomorphine utilization in Indian patients. Subjects who were assessed for ART for possible continuous dopaminergic therapy showed very good clinical benefits with apomorphine with average dosage for good benefit being around 3--5 mg. The side effects profile was in line with published literature. A bigger cohort could give better picture, down the time. It was also noted that the current concept of pretreating with domperidone for few days prior to the ART may not be much different from taking the medication on the day of ART. Vomiting and significant postural hypotension were the critical limiting factors for the ART. Other adverse events such as nausea, yawning, sleepiness, and dizziness, did not significantly deter from trying higher dosages, but could interfere in good clinical assessment.

Similarly, apomorphine pumps were well tolerated and gave significant clinical benefits by reduction in OFF periods and levodopa dosages. There were no clinically limiting adverse effects in the current therapy duration. A longer therapy duration and larger study sample will exudate the clinical limitations and benefits of apomorphine pumps in Indian sub-context. The main limitation noted was the cost, where in subjects currently need to spend around INR 800 to 1,500/day (USD: 12--25/day) depending upon the dosage required. Patients opted to reduce the dosage leading to suboptimal benefits or tried to reduce the duration of therapy/day. Few patients who were enthusiastic and enjoyed the clinical benefits discontinued therapy due to the costing factors. A good health insurance could help to overcome these hurdles for apomorphine utilization in India.

To conclude, apomorphine is a welcome addition for management of PD patients in India, especially those with significant motor fluctuations. It does have its own set of limitations, due to its cost, availability, technical issues, and pharmacological properties. However, its role in rescue therapies, effects on non-motor symptoms, and being a non-surgical method of continuous dopaminergic stimulation would be its strength in utilization.

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Conflicts of interest

There are no conflicts of interest.

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