Satellite Symposium Proceedings

A Landmark Year for Apomorphine – Advancing Parkinson’s Disease Management with New Clinical Evidence

Highlights of a Britannia-sponsored symposium held at the 21st International Congress of Parkinson’s Disease and Movement Disorders, Vancouver, Canada, 4–8 June 2017

Andrew Lees, Regina Katzenschlager and K Ray Chaudhuri

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Andrew Lees, 1 Regina Katzenschlager2 and K Ray Chaudhuri3


It has now been almost 30 years since the publication of the pivotal clinical trial in The Lancet in 1988, which confirmed that subcutaneous apomorphine (APO) has equivalent antiparkinsonian efficacy to levodopa for the management of ‘off’ symptoms in patients with Parkinson’s disease (PD). The study’s findings led to subcutaneous APO (APO-go®; Britannia Pharmaceuticals Ltd, UK) being licensed initially in the UK in 1993 for PD treatment and since that time it has been used successfully in clinical practice in Europe and many other parts of the world for the management of ‘off period’ disability. This symposium, chaired by Professor Andrew Lees (UK), who was a key investigator in that original trial, set out to review what has been another landmark year for APO and to discuss how recent clinical evidence can help inform our daily practice and improve outcomes for our patients with PD. APO is the only other drug with an antiparkinsonian effect equal to levodopa. When used as intermittent subcutaneous injections, it is also the most rapidly effective treatment for motor fluctuations and its efficacy has been confirmed in randomised trials. Extensive clinical experience and many uncontrolled studies have shown the efficacy of APO for the relief of motor fluctuations when administered either as an intermittent injection or as a continuous subcutaneous infusion using ambulatory mini-pumps, depending on the patient’s symptoms. However, unlike other therapies commonly used for these types of patients, such as levodopa/carbidopa intestinal gel and deep-brain stimulation, up to now Level 1 evidence for the efficacy and safety of APO infusion from large, randomised studies has been lacking. Professor Regina Katzenschlager (Austria) provided an overview of the clinical trial of apomorphine subcutaneous infusion in patients with advanced Parkinson’s disease (TOLEDO study), the first randomised, double-blind clinical trial to investigate the efficacy, safety and tolerability of APO-go 5 mg/ml solution for infusion compared with placebo in patients with PD whose motor fluctuations are uncontrolled despite optimised PD therapy. Results from this study will fill an important knowledge gap in the currently available evidence for APO infusion. Professor K Ray Chaudhuri (UK) went on to review the clinical indications for APO infusion and other continuous dopaminergic therapies, illustrated with patient case studies and supported by his experience since the 1990s in initiating and monitoring medication to obtain the best long-term results. Recently, wearable sensors have been used to monitor patients with PD undergoing treatment to help inform clinical management. Although APO is more than 150 years old, it is apparent that there are still many important lessons to learn about its mode of action and optimum clinical application which will be of benefit to patients with PD.

Keywords
Parkinson’s disease (PD), motor fluctuations, subcutaneous apomorphine infusion, randomised clinical trial

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Compliance with Ethics: Written informed consent was not obtained from the patient case included in this report; no identifying information or images have been used.

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Professor Lees introduced the symposium by highlighting that there had been several significant landmark events in the past year in the field of Parkinson’s disease (PD) and its treatment. Notably, it was now exactly 200 years since the original publication by James Parkinson of his *An essay on the shaking palsy*; 100 years since Tretiakoff discovered one of the most important lesions in PD, the loss of dopamine-producing cells in the substantia nigra and 50 years since the Hoehn and Yahr scale was first used to describe symptom progression in PD. In addition, 2017 was a landmark year for apomorphine (APO) as a PD therapy. One of the objectives of the symposium was to review information on this new treatment.

Professor Lees advised that APO had a long and interesting history in the field of neurology and PD (Figure 1). For those unfamiliar with APO, he said it was important to note that despite its name, it was not a narcotic substance. Since its discovery, APO has had various clinical applications in neurology, being used in the 19th century to treat chorea and pseudo-epilepsy, and at the beginning of the 20th century to treat delirium tremens due to alcohol or drug addiction. More recently, it has been used to treat erectile dysfunction. It was first suggested in the 19th century that APO might be a valuable potential treatment for PD but it was not until the 1950s that Schwab and colleagues, in the USA, reported positive results with subcutaneous administration of APO in patients with PD, despite some side effects (primarily nausea, vomiting and hypotension). Cotzias was instrumental in undertaking research that led to the development of levodopa as an oral therapy for PD but was aware of its limitations in many countries around the world for the management of ‘off period’ disability. However, despite extensive clinical experience and positive findings from many uncontrolled studies, Level 1 evidence from a randomised, controlled trial (RCT) had been lacking until now.

Professor Lees went on to introduce the international faculty. Professor Regina Katzenschläger, Head of the Department of Neurology and Karl Landsteiner Institute for Neuroimmunological and Neurodegenerative Disorders at the Danube Hospital in Vienna, Austria, is the principal investigator of the clinical trial of apomorphine subcutaneous infusion in patients with advanced Parkinson’s disease (TOLEDO study; NCT02006121), the first double-blind RCT to investigate the efficacy, safety and tolerability of APO-go 5 mg/ml solution for infusion compared with placebo in patients with PD whose motor fluctuations are uncontrolled despite optimised PD therapy.

Professor K Ray Chaudhuri, Director of the National Parkinson Foundation Centre of Excellence at Kings College London, has considerable experience in both clinical research and practical use of APO in patients with PD. Professor Chaudhuri would share his personal experience of how clinicians can optimise patient outcomes when they are treated with APO using a combination of careful patient selection, initiation and monitoring of treatment efficacy.

Figure 1: The history of apomorphine

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1869</td>
<td>Apomorphine first synthesised by Matthiessen and Wright</td>
</tr>
<tr>
<td>1870</td>
<td>Observations on apomorphine were reported in terms of benefits on involuntary movements</td>
</tr>
<tr>
<td>1870-1950</td>
<td></td>
</tr>
<tr>
<td>1951</td>
<td>Apomorphine first used in Parkinson’s disease</td>
</tr>
<tr>
<td>1967</td>
<td>Apomorphine shown to activate dopamine receptors</td>
</tr>
<tr>
<td>1967-1988</td>
<td>Apomorphine confirmed as a potential treatment</td>
</tr>
<tr>
<td>1970</td>
<td>The successful use of subcutaneous apomorphine in combination with domperidone reported</td>
</tr>
<tr>
<td>1979</td>
<td>Apomorphine confirmed with 50% reduction in ‘off’ periods up to five years later</td>
</tr>
<tr>
<td>1988</td>
<td>Efficacy of apomorphine confirmed with 50% reduction in ‘off’ periods up to five years later</td>
</tr>
<tr>
<td>1993</td>
<td>Apomorphine receives first European marketing license (UK)</td>
</tr>
<tr>
<td>2017</td>
<td>TOLEDO Study</td>
</tr>
<tr>
<td>2017-2020</td>
<td>Additional European and non-European marketing licences granted</td>
</tr>
</tbody>
</table>

Professor Lees advised that APO had a long and interesting history in the field of neurology and PD (Figure 1). For those unfamiliar with APO, he said it was important to note that despite its name, it was not a narcotic substance. Since its discovery, APO has had various clinical applications in neurology, being used in the 19th century to treat chorea and pseudo-epilepsy, and at the beginning of the 20th century to treat delirium tremens due to alcohol or drug addiction. More recently, it has been used to treat erectile dysfunction. It was first suggested in the 19th century that APO might be a valuable potential treatment for PD but it was not until the 1950s that Schwab and colleagues, in the USA, reported positive results with subcutaneous administration of APO in patients with PD, despite some side effects (primarily nausea, vomiting and hypotension). Cotzias was instrumental in undertaking research that led to the development of levodopa as an oral therapy for PD but was aware of its limitations in many countries around the world for the management of ‘off period’ disability. However, despite extensive clinical experience and positive findings from many uncontrolled studies, Level 1 evidence from a randomised, controlled trial (RCT) had been lacking until now.

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**A Landmark Year for Apomorphine in Parkinson’s Disease Management**

Andrew Lees

The National Hospital for Neurology and Neurosurgery and Reta Liya Weston Institute of Neurological Studies, Institute of Neurology, University College London, London, UK

**Introduction**

Parkinson of his, 100 years since was now exactly 200 years since the original publication by James Parkinson in his *An essay on the shaking palsy*; 100 years since Tretiakoff discovered one of the most important lesions in PD, the loss of dopamine-producing cells in the substantia nigra and 50 years since the Hoehn and Yahr scale was first used to describe symptom progression in PD. In addition, 2017 was a landmark year for apomorphine (APO) as a PD therapy. One of the objectives of the symposium was to review information on this new treatment.

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Professor Katzenschlager gave an introduction to the pharmacological properties of APO, a highly potent, short-acting dopamine agonist with broad spectrum receptor affinity for D1-like (D1, D5) and D2-like (D2, D3, D4) dopamine receptors, as well as serotonergic and adrenergic activity. When administered as an intermittent subcutaneous injection (APO-go PEN 10 mg/ml solution for injection), APO has a rapid onset of effect within 4–12 minutes and has been shown to reverse 95% of ‘off’ periods in patients with PD. Continuous subcutaneous APO infusion (APO-go 5 mg/ml solution for infusion) is indicated for the treatment of motor fluctuations (on–off phenomena) in patients with PD that are not sufficiently controlled by oral anti-PD medication. It is now licensed in 23 countries worldwide and has been used in clinical practice in the UK for more than 25 years.

Accumulated data from a considerable number of open-label studies undertaken over the past 20 years in patients with PD have demonstrated a mean reduction in daily ‘off’ time of around 60% and a mean reduction in dyskinesia intensity of around 32% following treatment with APO infusion. However, many clinical guidelines and systematic reviews, such as the evidence-based medicine review of treatments for the motor symptoms of PD issued by the International Parkinson and Movement Disorders Society, only include recommendations for the use of APO injection, since data from a randomised clinical trial providing Level 1 evidence for APO infusion have been lacking up to now. The phase III TOLEDO study was initiated to fill this evidence gap.

Professor Katzenschlager highlighted the significance of TOLEDO as the first double-blind, randomised, placebo-controlled, phase III study of APO infusion in this setting. The objectives of the study were to evaluate the efficacy, safety and tolerability of subcutaneous APO infusion in patients with PD with motor fluctuations not well controlled on optimised medical treatment. The study was undertaken in 23 centres in seven countries around Europe. Patients were eligible to participate in the study if they had had PD for >3 years (according to Queen Square Brain Bank Criteria) and an average ‘off’ time of >3 h/day with their motor fluctuations not adequately controlled on medical treatment (including ≥4 daily doses of levodopa) judged to be optimal by physician. Subjects also needed to be able to differentiate between ‘on’ and ‘off’ time, and ‘on’ time with troublesome dyskinesias and without troublesome dyskinesias in order to complete home diaries.

The design of the TOLEDO study is shown in Figure 2. A total of 107 patients were randomised 1:1 to APO infusion (n=53) or placebo infusion (n=54). After randomisation, patients underwent a treatment initiation phase of 5–10 days, followed by a dose adjustment phase (including oral medication) up to the end of week 4, and then stable treatment to the end of week 12. The target dose of APO was each patient’s individual optimised dose at hourly flow rates of 3–8 mg administered for 16±2 hours of their waking day. Following completion of the 12-week, parallel-group, double-blind, placebo-controlled phase, or in the case of withdrawal due to lack of efficacy, patients could enter a 52-week open-label phase.

The initial results of the 12-week double-blind phase had been presented at the 21st International Congress of the Movement Disorders Society in Vancouver, Canada, in June 2017. The open-label phase of TOLEDO is ongoing and results are expected in 2018.

Figure 2: Design of the TOLEDO study

![Figure 2: Design of the TOLEDO study](image-url)
Optimising patient outcomes with apomorphine – practical approaches to patient selection, initiation and monitoring

K Ray Chaudhuri
National Parkinson Foundation Centre of Excellence, Kings College London, Denmark Hill Campus, London, UK

In his presentation, Professor Chaudhuri discussed clinical and practical approaches to the use of APO infusion based on his 30-year experience with the use of this medication. He noted that key questions related to when patients with PD should be started on continuous dopaminergic drug delivery (CDD) therapy, how we decide which CDD therapy is best for each patient and, if APO infusion is selected, how we ensure it is optimised. In his view, the future of PD management would focus on personalised medicine for each individual patient to ensure the best outcomes.

Various CDD options are available in different countries around the world and generally comprise one of three choices. Levodopa/carbidopa intestinal gel (LCIG) is the continuous administration of levodopa/carbidopa by infusion into the duodenum/jejunum. It requires a gastrostomy procedure for the placement of the infusion tube. Deep-brain stimulation (DBS) is another option but this requires stereotactic brain surgery. Subcutaneous APO infusion is the least invasive option and is administered by means of a removable infusion pump which does not require surgery and is reversible. APO infusion can be initiated during inpatient hospitalisation or in an outpatient hospital setting.

The Navigate PD survey was a summary of expert opinion that was developed to aid clinicians when making a selection of one device-aided CDD therapy over another.

Professor Chaudhuri advised that the criteria for deciding whether patients were suitable for APO infusion had been outlined in the recent Expert Consensus Statement. These experts had agreed that APO infusion was suitable for patients with PD who had troublesome ‘off’ periods despite optimised treatment, and particularly in the following situations – patients who felt doses of APO intermittent injection were required too frequently, where dyskinesias limit further therapy optimisation, to simplify complex PD dosing regimens, as an alternative to surgical therapy or LCIG if these are contraindicated or because of patient preference, and when absorption or oral levodopa was impaired due to GI issues.

To help guide clinicians, particularly those who may be unfamiliar with using APO infusion, the Expert Consensus Statement also summarised the stepwise initiation process for patients who were starting treatment.

Although there were regional variations, Professor Chaudhuri noted that APO infusion could be initiated on either an outpatient or an inpatient basis. He advised that one-day initiation was common in the UK and was a cost-effective approach with support from PD nurse specialists (PDNS).

The initiation process comprised

1. patient selection and pre-treatment safety checks;
2. pre-medication, usually with domperidone;
3. treatment initiation;
4. dose optimisation/reduction of other PD medications; and
5. follow-up and monitoring.

Professor Chaudhuri considered that PDNS were key members of the multidisciplinary team involved in PD patient care, providing education, training and support to help ensure that each patient got the best from their selected therapy.
Once patients with PD were established on therapy, it was important that they were regularly monitored to ensure that treatment was effective and adjusted as necessary. Monitoring could be done in a variety of ways, including asking the patient how they feel about their therapy at clinic visits, asking them to keep a daily diary recording ‘on’ and ‘off’ periods, or using wearable monitoring devices or other sensors. Professor Chaudhuri stressed that the adjustment of any medication regimen was a dynamic process and could take time to get right, often several months.

Professor Chaudhuri concluded by saying that in his opinion, optimal outcomes with any PD therapy were best achieved with an individualised approach to treatment – selecting the right patient, giving the best treatment for them at the right time and continuing to monitor progress. He noted that PD progression was a complex process requiring personalisation of therapy to ensure patients receive the best treatment to suit their symptoms and lifestyle. Selection of treatment – aided by recommendations in treatment guidelines, supported by data from registries – should be individualised for each patient and their personal circumstances.

Wearable sensors could be used to support clinical opinion and decision-making in individual cases and help demonstrate why patients may need to change their treatment, but still require validation for use with device-aided therapies. In the case of APO infusion, optimising patient outcomes relied on careful patient selection, established stepwise initiation and continuous monitoring.

**Article highlights**

- The dopamine agonist apomorphine (APO) has an extensive history in the field of neurology and has been licensed (APO-go®, Britannia Pharmaceuticals Ltd, UK) and used successfully in clinical practice for almost 30 years for the effective management of motor symptoms in patients with Parkinson’s disease (PD).
- Positive clinical experience with APO has been supported by the results of many uncontrolled studies which showed its efficacy for the relief of motor fluctuations when administered either as an intermittent injection or as a continuous infusion.
- Until recently, Level 1 evidence from a randomised, blinded clinical trial to confirm the efficacy of APO infusion has been lacking.
- The clinical trial of APO subcutaneous infusion in patients with advanced Parkinson’s disease (TOLEDO study) is the first randomised, double-blind clinical trial to investigate the efficacy, safety and tolerability of APO-go 5 mg/ml solution for infusion compared with placebo in patients with PD whose motor fluctuations are uncontrolled despite optimised PD therapy.
- In clinical practice, optimal outcomes with APO infusion, or any other form of continuous dopaminergic stimulation, are best achieved with a personalised approach to therapy – selecting the right patient and continuing to monitor progress.
A Landmark Year for Apomorphine in Parkinson’s Disease Management

When the increasing frequency and severity of daily ‘OFFs’, dyskinesias or pill burden threaten everything they live for,1,2 it’s time to prescribe APO-go PUMP3 – continuous subcutaneous infusion of apomorphine, delivering smooth, predictable control of motor fluctuations.3,5

When increasing ‘OFFs’ and dyskinesias begin to dominate...