New Perspectives in Non-oral Drug Delivery in Parkinson's Disease

Highlights of a Satellite Symposium Held at the XX World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, 8–11 December 2013

Werner Poewe,[1] Andrew Lees,[2] K Ray Chaudhuri[3] and Stuart Isaacson[4]

1. Professor of Neurology, Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; 2. Professor of Neurology, The National Hospital for Neurology and Neurosurgery, Queen Square and Emeritus Director, Reta Lila Weston Institute of Neurological Studies, University College London, Institute of Neurology, London, UK; 3. Professor of Movement Disorders, Director National Parkinson Foundation Centre of Excellence, Kings College, Denmark Hill Campus, London, UK; 4. Associate Professor, Florida International University, Herbert Wertheim College School of Medicine, Miami; Director, Parkinson's Disease and Movement Disorders Center of Boca Raton; Research Director, Marcus Neuroscience Institute, Boca Raton Regional Hospital, Boca Raton, Florida, US

Abstract

Oral therapies, including levodopa, dopamine agonists and monoamine oxidase type B (MAO-B) inhibitors, form the mainstay of medical treatment for Parkinson's disease (PD). However, over time, chronic treatment with multiple daily doses of oral agents is often associated with the development of motor fluctuations and dyskinesias. Alternative methods of dopaminergic drug delivery, particularly if they bypass the gastrointestinal system, may be of value for PD patients who have developed motor complications despite optimised oral therapy, in particular those with gastrointestinal absorption issues, including gastroparesis. This satellite symposium, held at the XX World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, from 8–11 December 2013, was chaired by Professor Werner Poewe (Austria) and Professor Andrew Lees (UK) and discussed recent evidence regarding the benefits of using non-oral drug-delivery strategies with therapies such as subcutaneous apomorphine. Beginning with the history of apomorphine and its well-established use in PD both as an intermittent injection and a continuous infusion, the presenters set out the evidence for its efficacy in managing both motor and non-motor symptoms in PD. The significance of gastrointestinal involvement in PD and how this may influence responses to oral medications was also reviewed. Interim results from the ongoing Apokyn for Motor IMProvement of Morning AKinesia Trial (AM IMPAKT) study of the use of subcutaneous apomorphine in PD patients with morning akinesia were also presented and the continuing main role of apomorphine in the treatment of PD was discussed, including the selection of the most appropriate patients for this effective yet underused therapy.

Keywords

Parkinson's disease (PD), motor fluctuations, dyskinesia, morning akinesia, gastroparesis, subcutaneous apomorphine

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Correspondence: Werner Poewe, Department of Neurology, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria. E: werner.poewe@i-med.ac.at

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Parkinson's disease (PD) is a progressive neurodegenerative disorder, characterised by motor features but is also associated with a broad spectrum of non-motor symptoms (NMS). Oral levodopa, dopamine agonists or monoamine oxidase type B (MAO-B) inhibitors, given as monotherapy or in various combinations, form the basis of medical treatment for PD. However, chronic treatment with these oral therapies is often associated with the development of motor fluctuations as well as drug-induced dyskinesias, presenting a particular problem in the management of PD patients as their disease progresses.

This satellite symposium (held at the XX World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, 8–11 December 2013) focused on new perspectives in non-oral drug delivery in PD, including the significance of gastrointestinal (GI) absorption factors, as well as the background behind apomorphine therapy and the effectiveness of subcutaneous apomorphine intermittent injection for rapid relief of 'off' episodes, or apomorphine infusion which provides the patient with continuous dopaminergic drug delivery (CDD). Also highlighted was emerging evidence from ongoing clinical studies

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(Apokyn for Motor IMProvement of Morning AKinesia Trial [AM IMPAKT]) that subcutaneous apomorphine injection can have a positive effect on morning akinesia by reducing motor complications in patients receiving conventional oral therapies and also results in significant improvements in patients' quality of life (QoL). The final panel discussion centred on the current and future role of subcutaneous apomorphine in the management of advancing PD, and the selection of patients most suited to each formulation. ■

The History of Apomorphine in Medicine and its Clinical Use in the Treatment of Parkinson's Disease

Andrew Lees

National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

Apomorphine has been available for the treatment of PD for a quarter of a century and although it has a long and interesting history, this effective drug still appears to be underused in clinical practice for the treatment of PD. Apomorphine was first synthesised by German and British chemists in the nineteenth century and despite the suggestion in its name, in contrast to morphine, it is not a narcotic but a powerful dopamine receptor agonist stimulating D1, D2 and D3 receptors.

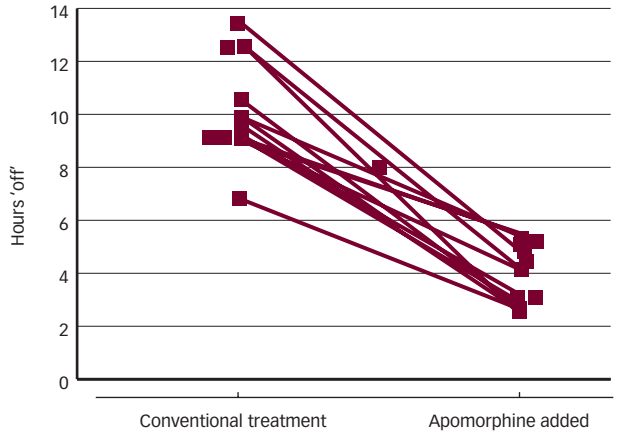
Apomorphine was first used by veterinary surgeons to treat behavioural vices in domesticated animals before its emetic properties were exploited as a treatment for poisoning. At high doses apomorphine was found to cause involuntary movement and stereotyped behaviour, such as punding, but at lower doses it had a beneficial therapeutic effect – this was the first evidence that different doses could produce different outcomes. These stereotypical, repetitive behaviours have more recently been reported in PD patients treated with dopamine agonists and levodopa, particularly at high doses.[1,2]

In clinical practice, apomorphine has been investigated for the treatment of a wide range of indications over the years. Neurologists first used apomorphine to treat Sydenham's chorea in 1870, and later to treat pseudoseizures. It was not until the 1880s that it was used to treat muscle spasm. By 1900 apomorphine was utilised in the treatment of alcohol and opiate addiction, as well as insomnia, by the 1930s for neurosis and in the 1960s for sexual dysfunction. Psychiatrists also recommended apomorphine as a sedative and antipsychotic and as an effective treatment for alcoholism and substance abuse.

Schwab and colleagues in the US were the first to demonstrate the anti-Parkinsonian properties of apomorphine in 1951.[3] They showed that apomorphine, though very short lived in its effect and with some side effects (nausea, vomiting and falls in blood pressure), could relieve rigidity and tremor for periods of up to 30–40 minutes. George Cotzias, following his seminal papers on the efficacy of high-dose levodopa in PD in the late 1960s, suggested after a number of careful clinical studies that apomorphine may have value as a clinical investigational tool, improve tremor refractory to dopamine and reduce dyskinesias, as well as possibly being antipsychotic.[4,5]

Clinical pharmacological studies showing that the 'on-off' syndrome could be markedly reduced by continuous intravenous levodopa therapy and that single subcutaneous injections of apomorphine could reverse 'off' periods led to hope that the duration of benefit from long-term levodopa therapy could be extended.

Figure 1: Effect of Apomorphine Given by Infusion Pump on Mean Hours of 'Off' Periods per Day Averaged Over One Week



Source: Reproduced with permission from Stibe et al. 1988.[6]

The technological development of ambulatory mini pumps for the management of brittle diabetes and the discovery of the peripheral dopamine antagonist, domperidone, paved the way for new clinical pharmacological trials of apomorphine at University College London in 1987. This work showed that single injections of apomorphine could be used as a rescue therapy for patients with one or two refractory 'off' periods and that continuous waking day subcutaneous apomorphine markedly reduced the frequency and duration of 'off' periods (reduced from 10 hours 'off' per day to 3–4 hours 'off' per day). Intermittent injections were able to switch patients 'on', thus restoring their functional independence (see *Figure 1*).[6] Following publication of these results in 1988, other groups replicated these findings and it was concluded that apomorphine was the only clinically available dopamine agonist that was equipotent to levodopa and it was subsequently licensed for the treatment of PD in the UK.

Over the last 25 years apomorphine has been confirmed to be a highly effective therapy for refractory motor fluctuations, including dyskinesias, and thousands of PD patients throughout the world have benefited from its use. It is now known that apomorphine stimulates all the dopamine receptor subtypes – D1, D2 and D3. Research continues to investigate the clinical safety of alternative routes of apomorphine administration (including oral) but improved infusion pump technology and the use of new Teflon-coated needles have increased long-term adherence to this regimen, particularly by alleviating the severity and morbidity of abdominal

wall panniculitis such that skin nodules need no longer be a limiting factor for subcutaneous apomorphine. Further studies are required to confirm whether apomorphine may have a lower tendency to induce psychosis and impulse control disorders (ICDs) than other dopaminergic drugs.

Interest in the wider role of apomorphine continues today and a recent study demonstrated an improvement in memory and reduced amyloid deposition in transgenic murine Alzheimer's disease models given subcutaneous apomorphine injection, raising the possibility that apomorphine might actually promote amyloid beta degradation in this setting.[7] ■

How Does Apomorphine Compare to Other Continuous Drug-delivery Strategies? Motor and Non-motor Data

K Ray Chaudhuri

King's College and Imperial College, London, UK

Ideally, specialist centres treating PD should be able to offer patients the complete range of available non-oral treatments: subcutaneous apomorphine infusion and injection and intrajejunal levodopa (IJL) infusion, as well as the surgical procedure of deep brain stimulation (DBS) and transdermal therapies, allowing them to make an informed choice in the management of their condition.

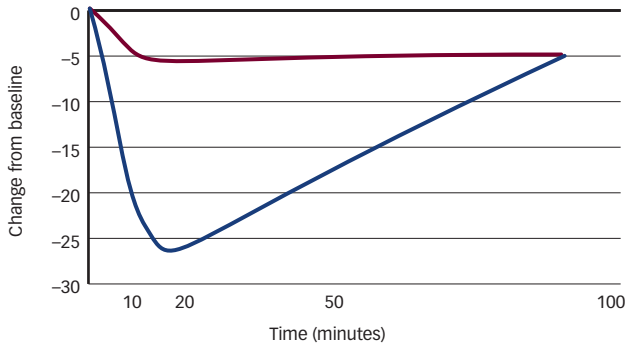
Transdermal rotigotine has been shown to reduce 'off' periods,[8] as well as having beneficial effects on motor function (as measured by UPDRS III), nocturnal akinesia, nocturia and early morning 'off'.[9] IJL infusion also has a robust effect on motor function, with studies showing that it reduces 'off' periods, with the effect persisting for up to 12 months, and achieves a reasonable reduction in levels of dyskinesia.[10]

Extensive clinical experience with subcutaneous apomorphine, both as an injection and as an infusion, has shown that its effects can be dramatic in treating dyskinesias in PD patients. Studies demonstrate that subcutaneous apomorphine injection leads to robust improvement in motor state, with a single dose causing a predictable improvement in UPDRS motor score compared with placebo (see *Figure 2*).[11,12] A review of largely open-label studies of apomorphine infusion revealed reductions of 60.8 % in 'off' periods, 35.6 % in dyskinesias and 47.5 % in levodopa dose.[13] A significant reduction in dyskinesia threshold has also been shown with apomorphine.[14]

In addition to the motor symptoms, a broad range of NMS impair and compromise health-related QoL and aggravate caregiver stress in PD. Like motor symptoms, NMS fluctuate and these fluctuations also appear to be related to pulsatile dopamine delivery. Fluctuating levels of dopamine with oral therapies are exacerbated in the advanced stages of PD, as gastric emptying becomes erratic and swallowing becomes difficult. There is increasing evidence that CDD can improve NMS in PD, particularly the dopaminergic NMS, as well as those that are part of non-motor fluctuation. For patients with moderate to advanced PD, the most potent CDD is achieved using subcutaneous apomorphine infusion or IJL/carbidopa infusion (duodopa). Data are now available to indicate that both therapies are also effective for the management of NMS in PD patients.

A recent review of published literature on apomorphine and NMS showed varying beneficial effects on symptoms such as hyperhidrosis, contrast sensitivity in the eye, nocturnal discomfort, early-morning 'off' periods, cognition, psychosis, bladder disturbances and sleep problems.[15] In particular, Martinez-Martin[16] showed that apomorphine was effective on aspects of sleep, including restless legs, sleep onset insomnia and fatigue. Apomorphine also demonstrated beneficial effects on aspects of mood, particularly nervousness, sadness and anhedonia.[15] In the case of ICDs, rates would appear to be low with apomorphine (9.7 %), with only 2.4 % requiring discontinuation of therapy.[15] There is some evidence suggesting the possibility of an antipsychotic effect of apomorphine[17] and also that apomorphine is tolerated in patients with visual hallucinations.[15,18]

Figure 2: Subcutaneous Apomorphine Injection (Blue) Leads to Improvement in Motor State Compared to Placebo (Red) as Shown by UPDRS Motor Score



UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Adapted from Pfeiffer et al. 2007.[11]

In terms of other autonomic symptoms, apomorphine has good effects on dysautonomia, particularly troublesome (and frequently socially isolating) symptoms such as dribbling of saliva, as well as swallowing and constipation.[16] Apomorphine also has an impressive effect on urinary dysfunction, in particular frequency and urgency and to some extent nocturia, possibly driven by its D1 receptor activity.[16]

The EuroInf study is a multicentre, European case-controlled trial comparing apomorphine and IJL infusion in patients with advanced PD.[19] The results showed that in the 44 IJL infusion patients and 43 apomorphine infusion patients both drugs had a robust effect size (1.69 for IJL and 0.87 for apomorphine). QoL was significantly improved with a large effect size for both therapies. In terms of adverse effects, follow-up data at three years show more device-related problems with IJL infusion, as well as concerns with demyelinating polyneuropathy. There were no ICDs observed in the IJL arm. In the apomorphine arm, the only concern was severe somnolence. Incident ICD occurred in two cases on apomorphine, though several other patients had pre-existing ICD that actually improved.

Further research is ongoing and the planned randomised, double-blind Clinical Trial of Apomorphine Subcutaneous Infusion in Patients With Advanced Parkinson's Disease (TOLEDO) study (25 centres in seven countries) will have the primary objective of investigating the efficacy of subcutaneous apomorphine infusion compared with placebo in PD patients with motor fluctuations not well controlled on medical treatment. The aim of the TOLEDO study is to provide Level 1 evidence for the efficacy of apomorphine in this setting and the results are awaited with interest. ■

Gastrointestinal Dysfunction, Delayed Levodopa Onset and Morning Akinesia – Apomorphine Injection for Morning Akinesia – The AM IMPAKT Trial Interim Data

Stuart Isaacson

Parkinson's Disease and Movement Disorders Center of Boca Raton, Florida, US

In patients with PD, motor and NMS are frequent during 'off' periods, especially when the next levodopa dose has a delayed onset of action (delayed 'on'). Delayed 'on' of the first daily dose of levodopa is known as morning akinesia, and this can have a significant impact on a patient's daily activities and impair their QoL.[20] Morning akinesia can be due to delay in gastric emptying, impaired intestinal absorption or pharmacodynamic effects. Morning akinesia is common in PD patients, as most patients have some degree of bradykinesia on awakening. Unfortunately, even in patients with prolonged morning 'off' periods, morning akinesia is not always routinely queried nor recognised.

GI function is under control of the central, autonomic and enteric nervous systems. Involvement of the GI system in PD has been well described resulting in multiple GI symptoms, although its effect on levodopa response has not been as well recognised. The entire length of the GI tract is involved, including salivary glands, oesophagus, stomach, small intestine, colon and rectum (see *Figure 3*). GI dysfunction in PD is often present at or prior to diagnosis, and persists throughout the disease course, frequently worsened by dopaminergic and other concomitant medications.

Gastroparesis (delayed emptying of the stomach) is common in patients with PD.[21] A survey of PD patients found that 24 % reported nausea and 45% reported bloating, both symptoms of gastroparesis.[21] As well as compounding NMS and affecting QoL,[16] gastroparesis can also cause delayed time-to-on (TTO) and morning akinesia. Other symptoms of gastroparesis, such as early satiety, weight loss and malnutrition, may not be present. Thus, presence of delayed-on or morning akinesia should prompt consideration of delayed gastric emptying of levodopa dose.

This major feature of gastroparesis in PD, delayed TTO, is due to the delay in emptying of levodopa from the stomach into the proximal small intestine where it is absorbed. This can also result in suboptimal-on and in dose failure (so-called 'no-on'). Delayed gastric emptying can also delay and lower the levodopa peak, which may prolong the duration of the 'on' response.[22]

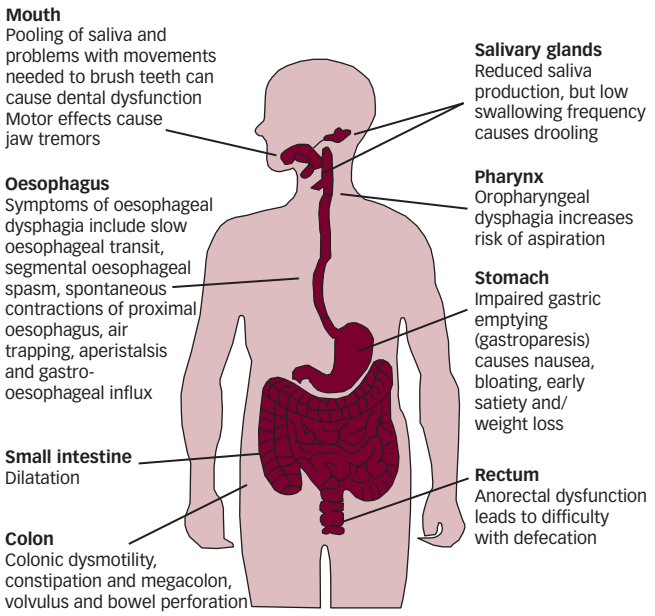
Pharmacological treatments for gastroparesis are limited in PD. Prokinetics, such as domperidone, may be used but metoclopramide cannot as it worsens parkinsonism. Erythromycin results in rapid tachyphylaxis limiting its usefulness, although other experimental motilin agonists are being studied. Lubiprostone may help constipation in PD,[23] but its effect on gastric emptying has not been evaluated. Injection of botulinum toxin into the pylorus has been successful in some patients.[24] A gastric pacemaker has also been useful for gastroparesis, but has not been studied in PD.[25]

Delivery of dopaminergic therapy by a non-oral route is important to consider in patients with PD and gastroparesis. Subcutaneous apomorphine injection has been used by patients with PD in the 'off' state to provide a rapid and reliable TTO, resulting in significant improvement at 10 minutes versus placebo.[11] The ongoing AM IMPAKT trial is a phase IV, multicentre, multiple-treatment, open-label efficacy and safety study in PD subjects with delayed onset of levodopa effect upon awakening (morning akinesia). The trial will also evaluate the frequency of delayed gastric emptying in a subgroup of patients. The study will include 100 subjects across 10 sites in the US. The major endpoint is change from baseline in average daily TTO, while secondary endpoints include changes in the Hoehn and Yahr stage, Clinician and Patient Global Impression of Severity and QoL as measured using the EQ-5D-3L index score and the EQ-5D-VAS visual analogue scale.

Interim analysis of the initial 37 patients in the AM IMPAKT study revealed that morning akinesia is common and occurs throughout the course of PD. Most patients reported 36–48 month duration of morning akinesia despite adjunctive therapies. Enrolled patients had never used apomorphine treatment , despite having prolonged duration of morning akinesia and pen injection being commercially available for almost 10 years.[26] Identification of optimal dose, defined as achieving 90 % of the levodopa response within 15 minutes, found 4 mg apomorphine in 40 % of patients with 20 % requiring doses above 4 mg.

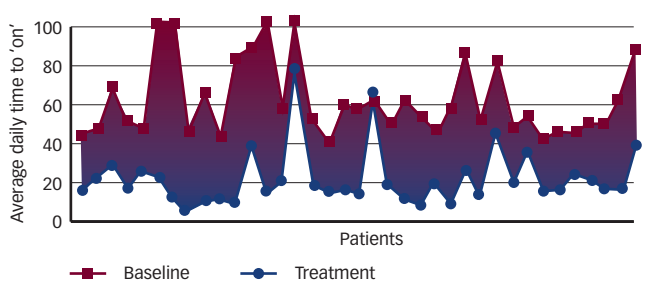
Apomorphine significantly improved the primary endpoint of TTO by an average of 40 minutes, reducing from a mean of 62.05 minutes at baseline to a mean of 23.25 minutes at the end of the apomorphine treatment period ($p<0.0001$). Of the 37 patients enrolled in the study at interim analysis, apomorphine response was highly reliable with 36/37 achieved a significant reduction in TTO. In *Figure 4* each of the paired red squares and blue dots represents a single patient, where the red square is the mean delay in TTO over 7 days on levodopa and the blue dot below is the same patient's mean TTO over the next 7 days using the apomorphine pen. The improvement in many patients was dramatic – for example, one patient went from 45 minutes to turn 'on' to 18 minutes to turn 'on', others went from dose failure to turn 'on' in just over 20 minutes. These results show that apomorphine does not just achieve a statistical difference when patients are averaged together, but that practically every patient sees a meaningful and rapid clinical improvement.

Figure 3: In Parkinson's Disease the Entire Length of the Gastrointestinal Tract is Dysfunctional



Source: Reproduced with permission from Pfeiffer 2003.[21]

Figure 4: Change from Baseline in Average Daily Time-to-on (Evaluated by Patients)



Each pair of red squares and blue dots represents a single patient: the red square is the mean delay in time-to-on (TTO) over 7 days on levodopa (baseline); the blue dot is the same patient's mean TTO over the next 7 days using apomorphine injection.

Source: Isaacson et al. 2013.[26]

In terms of health-related QoL, EQ-5D-3L index scores were significantly reduced from a mean of 3.50 at baseline to a mean of 2.22 at the end of the treatment period ($p<0.0001$). EQ-5D-3L is a patient-reported health outcome scale related to mobility, self-care, usual activities, pain/discomfort and anxiety/depression and each dimension is ranked from 1 (no problem) to 5 (extreme problem) so lower scores indicate a more favourable rating. Similarly, EQ-5D VAS scores significantly improved from a mean of 46.72 at baseline to 64.44 at the end of the treatment period ($p=0.0003$). Using this scale, subjects rate their health state relative to akinesia on a scale of 0 (worst imaginable) to 100 (best imaginable) so higher scores indicate a more favourable rating. Both patient- and clinician-rated impact of morning akinesia on QoL also showed significant improvement, and overall tolerability of apomorphine was good. Analysis of the gastroparesis subgroup is ongoing and initial data suggest that bloating and early satiety were common at baseline in these patients on the Gastroparesis Cardinal Symptom Index, and that the GI and urinary domains on Scales for Outcomes in Parkinson's Disease (SCOPA)-autonomic were significant.

These interim results from the AM IMPAKT study demonstrate that morning akinesia is a common but under-recognised symptom of PD. Subcutaneous apomorphine pen injection results in a rapid and reliable TTO in these patients with significant improvement in QoL. Subcutaneous apomorphine pen injection for the management of morning akinesia seems under-utilised by many patients and their physicians. ■

Panel Discussion – Apomorphine in Parkinson's Disease – When and Who in Clinical Practice?

Asked about the value of apomorphine in establishing the diagnosis of PD in difficult patients, Andrew Lees noted that in the UK the use of response tests is somewhat controversial but apomorphine has the advantage of being quicker than a levodopa response test. It is therefore particularly useful for geriatricians since it can be undertaken in day centres. Apomorphine is not a diagnostic test for PD, however it is useful in assessing dopaminergic responsiveness in an individual patient, both at the beginning of the disease and throughout its course.

Ray Chaudhuri stressed that even when PD has progressed it is useful to review responsiveness to dopaminergic drugs and also to establish the dyskinesia threshold. Stuart Isaacson noted that studies have shown that levodopa requires a couple of weeks to build up a robust response whereas apomorphine, perhaps by bypassing the oral route or maybe just because of its potency, seems to show a more rapid and reliable improvement.

With regard to selecting suitable non-oral treatment for PD patients, Werner Poewe, along with Ray Chaudhuri, firmly believes that apomorphine is not used enough. Asked what the indicators are for apomorphine versus the other non-oral treatments, Ray Chaudhuri emphasised that whether to use apomorphine, Duodopa® or DBS depends on local expertise – it is vital to have the support of a multidisciplinary team, in particular a nurse specialist. If this support is in place then there is no reason why one treatment cannot be used over another.

Werner Poewe considered that it is important to inform patients of the therapeutic options available and offer them a choice of treatment. He stressed that when treating fluctuations there will always be remaining 'off' periods and the problem of delayed 'on' whichever drug regimen is used. It is therefore convenient for patients to be equipped with an apomorphine pen that they can use on demand. The apomorphine pen is under-used in Werner Poewe's view, perhaps due to a lack of awareness of it benefits among physicians.

Andrew Lees noted that in the UK many colleagues use a dispersible form of levodopa in this situation, but this takes time to have an effect. Ray Chaudhuri noted that while many colleagues worry about patient-administered injections such as apomorphine they are happy to recommend patients with diabetes for insulin injections without hesitation. Ray Chaudhuri believes that neurologists are conservative in this sense so the message emphasising the usefulness and effectiveness of apomorphine must be communicated.

Stuart Isaacson agreed, noting that the motor effects of apomorphine are as robust as those of levodopa, and may be superior in many patients. Inexperience in using the apomorphine intermittent injection pen, fear of injection needles and other factors may seem like barriers to its use, but better recognition of morning akinesia and delayed TTO should prompt strong consideration of its use. Stuart

Isaacson stressed that virtually all PD patients will have 'off' periods and many do not turn 'on' reliably, and also that most patients have some degree of morning akinesia (and have probably have had it for several years). It is therefore a matter of asking patients the right questions to identify the clinical need for the apomorphine pen and then encouraging patients to try it.

Werner Poewe agreed, noting that while titrating the apomorphine dose can take a little time, it is a highly effective therapeutic strategy that remains chronically under-used. It is hoped that new data from ongoing studies, such as AM IMPAKT, and future studies including TOLEDO, will allow apomorphine to become achieve greater recognition as a valuable treatment for PD. ■

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