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Apomorphine therapy in Parkinson's disease and future directions

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ABSTRACT

Apomorphine infusion or injection is an important dopamine agonist non-oral therapy usually used in advanced Parkinson's disease (PD) with refractory motor fluctuations. The drug also has appreciable efficacy for nonmotor fluctuations and is the quickest to reverse predictable "off" periods. Current subcutaneous administration, however, is complicated by problems associated with needle-based therapies, such as skin nodule formation, skin irritation, and avoidance of this treatment option by needle-phobic subjects.

In this review we focus on what the future might hold for apomorphine injection/infusion. We discuss interesting and novel delivery strategies of apomorphine or esters via oral, buccal, inhalation and a novel pump-patch route. We also discuss recent research that has highlighted some important properties of apomorphine in animal models, such as a potential anti-amyloid effect and its potential impact in the management of PD dementia or perhaps even Alzheimer's disease. A potential role for apomorphine infusion in cases with impulse control disorders and other nonmotor issues is also discussed.

1. Introduction

Apomorphine therapy for Parkinson's disease (PD) has a rich and extensive past, being described as useful for the management of PD by Weil in the 19th century. Fast forwarding, Schwab et al. reported that apomorphine hydrochloride attenuated tremor and rigidity in PD patients, a finding that has been successfully translated to clinical therapy for PD in the 20th century [1–5]. This short review focuses on what the immediate and more distant future may bring in terms of apomorphine therapy for PD, in terms of delivery systems as well as efficacy for management of some symptoms regarded as key unmet needs in PD.

2. The immediate future

2.1. The TOLEDO study

This will entail the release of the data from the TOLEDO study (ClinicalTrials.gov Identifier: NCT02006121), a multicenter, parallel-group, double-blind, placebo-controlled phase III study that was designed to evaluate the efficacy and safety of subcutaneous apomorphine infusion in PD patients with complicated motor fluctuations refractory to conventional medical treatment. The study was conducted in 7 countries and 23 hospitals. Recruitment and enrolment are completed and outcome data are being analyzed. It is expected that there will be a greater reduction of "off" periods in the apomorphine arm compared with placebo, but the secondary efficacy variables, such as the effect of apomorphine versus placebo on the nonmotor symptoms scale of PD (NMSS), both in relation to the individual domains and total score, also will be of great interest. This is because several open-label and comparative studies point towards the efficacy of apomorphine on some nonmotor symptoms such as sleep, mood and nonmotor fluctuations [6–8].

3. Apomorphine delivery strategies: what does the future hold?

The subcutaneous route has been the mainstay for apomorphine therapy, either as a pen delivered injection or continuous infusion. Although effective, skin nodules complicate such therapy and in some cases become problematic. For some patients, the treatment cannot be used because of needlephobia. The development of alternative routes of delivery of apomorphine is, therefore, an

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Fig. 1. Device for inhaled administration of apomorphine.

unmet need and strategies are being developed.

3.1. Inhaled apomorphine

One such route is the pulmonary route in which apomorphine is administered by an inhaler device (Fig. 1). The pulmonary route bypasses the gastrointestinal tract and provides rapid delivery of the drug to the central nervous system. This is further aided by the fact that the pulmonary system is highly vascular. An inhaled version of apomorphine (VR040) has been developed and has been utilized in a phase 2, placebo-controlled, double-blind clinical trial at a single center in the UK (ClinicalTrials.gov Identifier: NCT01683292). The product is aimed at a quick rescue from "off" periods and, in the clinical trial, 3 doses (0.2, 0.5 and 0.8 mg) were studied. At 0.5 and 0.8 mg "off" was reversed and "on" state was achieved at 40 and 20 min respectively; the product was well-tolerated [9]. A subsequent study, with higher doses up to 4 mg, showed good efficacy with a peak plasma level at 2–7 min after inhalation and "off" period reversal at a mean of 10 min. Long-term efficacy data and multicenter trials are still required, but inhalation may become a feasible delivery route for apomorphine rescue therapy in the future [10]. Pulmonary irritation on long term exposure and the ability of PD patients to handle the inhaler device during severe motor "off" periods remain concerns.

3.2. Apomorphine via the patch pump technology

The transdermal patch-pump is a technology where a mini-pump is attached to a skin patch and delivers the drug via the transdermal route (Fig. 2). The method has been utilized for levodopa delivery and an apomorphine product (ND0701) has been developed for use by this route in advanced PD as an alternative option to apomorphine infusion. The safety and tolerability of this delivery system needs to be further established.

3.3. Apomorphine via the sublingual route

A buccal formulation of apomorphine (APL-130277) is being developed for use as a rescue medication in overcoming "off" periods (Fig. 3). The product is a thin-film strip containing apomorphine in a bilayer (to avoid oral irritation) and patients are instructed to keep the film under the tongue for the drug to be absorbed through the oral cavity for rapid delivery. In initial studies, 15 of 19 patients studied experienced reversal of their "off" periods within 30 min (average time to full "on" was 22 min) with the "on" lasting for a mean duration of 50 min [11]. No major adverse events have been reported and there is no report as yet of any problematic mucosal irritation in the mouth. Phase 3 trials with APL-130277 are now under way in doses ranging from 10 to 30 mg in what promises to be an important new development for rescue therapy in PD (ClinicalTrials.gov Identifier: NCT02469090).

Another sublingual device, delivering a buffered solution of apomorphine (RN-101, Apotone) is also being developed. Using buffered solutions at a pH of 7.6 in an early trial the product, which is delivered by a dual chambered device, has shown time to T-max and C-max being comparable to a single dose of subcutaneous apomorphine.

3.4. Oral delivery of apomorphine and derivatives

Oral therapy with apomorphine could avoid many of the problems associated with a needle based subcutaneous therapy, but intestinal absorption of apomorphine remains a key problem. Borkar et al. [12] used a Caco-2 monolayer that is grown on a filter support and is known to be a good model for assessing intestinal permeability and have shown that of two apomorphine esters, monolauroyl apomorphine (MLA) and dilauroyl apomorphine (DLA), MLA can be transported and DLA needs to be converted to MLA for transport. Another study has described the beneficial motor effects of the orally active compound, R-(-)-11-*O*-valeryl-*N*-*n*-propylnoraporphine, in 1-methyl-4-phenyl-1,2,3,6-

Fig. 2. A patch-pump device for delivery of the drug via subcutaneous route.