Pérez Lloret, Santiago

Apomorphine for the treatment of refractory motor fluctuations in late stage Parkinson's disease : an old drug revisited

Preprint del documento publicado en European Journal of Neurology, 2013

Este documento está disponible en la Biblioteca Digital de la Universidad Católica Argentina, repositorio institucional desarrollado por la Biblioteca Central "San Benito Abad". Su objetivo es difundir y preservar la producción intelectual de la Institución.

La Biblioteca posee la autorización de los autores y de la editorial para su divulgación en línea.

Cómo citar el documento:

Pérez Lloret, S. Apomorphine for the treatment of refractory motor fluctuations in late stage Parkinson's disease : an old drug revisited [en línea]. Preprint del documento publicado en *European journal of neurology* 2013. doi:10.1111/ene.12113.

Disponible en :<http://bibliotecadigital.uca.edu.ar/repositorio/investigacion/apomorphine-treatment-refractory.pdf>
[Fecha de consulta:]

Apomorphine for the treatment of refractory motor fluctuations in late stage Parkinson's Disease: an old drug revisited.

Santiago Perez-Lloret MD PhD

Department of Clinical Pharmacology, Toulouse University Hospital & Clinical Pharmacology & Epidemiology Laboratory, Buenos Aires Catholic University.

Apomorphine is the oldest dopaminergic agent and was initially known for its emetic properties [1]. Although Weill suggested using it to treat Parkinson's disease (PD) in 1884 [2], evidence about its antiparkinsonian efficacy was provided initially by Schwab and colleagues in 1951 and then by Cotzias and co-workers in 1970 [3]. Subcutaneous injection of the drug displayed potent but short-live antiparkinsonian effects usually at the expense of vomiting and postural hypotension. These limitations coupled with the advent of orally-active dopamine receptor agonists led to a waning in the interest in the drug [3].

Apomorphine is the most potent dopamine agonist with a 10-fold greater affinity for D1 and D2 receptors than dopamine [2]. It also has some moderate affinity for alpha-adrenergic 1D, 2B and 2C receptors and for serotonin 5HT_{1A}, 5HT_{2A}, 5HT_{2B} and 5HT_{2C} receptors.

Subcutaneous injection or infusion represent the only currently approved apomorphine formulations [4]. After injection, absorption is rapid and complete, mean latency to motor response is about 11-13 minutes and duration of action is about 56-62 minutes [4]. Several randomized double-blind controlled clinical trials lend support to the use of subcutaneous apomorphine as a rescue medication [2,4]. In one of the most recent studies, apomorphine single injections significantly reduced motor Unified PD Rating Scale scores at 10 and 20 minutes after administration as compared to placebo [2]. Such effects persisted for 6 months. Symptomatic effect of continuous apomorphine infusion

is similar to that of levodopa, with a reduction of “off” periods up to 80% in some cases [5]. Diskinesias may also be reduced after infusion [5], thus highlighting its utility in late stage PD patients suffering from motor fluctuations.

Yawning, dizziness and nausea are the most commonly observed adverse events [4]. QTc prolongation, orthostatic hypotension and cardiac events can also be observed. Granulomas or subcutaneous nodules at the injection site can be observed in up to 10% of patients after long-term use. Injection site rotation is recommended to avoid such reactions. As with any other dopamine agonists, impulse-control disorders can also be observed [6].

Apomorphine injections or infusion are not easy to manipulate and are related to cutaneous adverse events, which prompted the exploration of alternative administration routes [2]. In general, safety issues have been major limitations to many of such routes [2]. For example, intravenous infusions resulted in intravascular thrombosis and formation of apomorphine crystals within the cardiovascular system in 3 out of 6 patients, whereas sublingual administration led to severe stomatitis in 50% of the subjects in one study. Similarly, disabling nasal irritation and vestibulitis were sometimes observed with intranasal spray formulations.

Grosset and colleagues report in this issue of the journal the results of a proof-of-concept efficacy and safety study of single doses of a recently developed inhaled apomorphine formulation [7]. Twenty-four PD patients with motor fluctuations, mainly end-of-dose wearing-off, took part in this randomized, double-blind, placebo-controlled study. There were no differences in the proportion of patients who reported being in an ‘on’ state at any time after placebo or inhaled apomorphine 0.2 mg, 0.5 mg or 0.8 mg doses. However,

there was a suggestion of benefit at the higher doses (5 out of 12 patients switched 'on' at the 0.5 or 0.8 mg doses, versus 1 out of 6 for placebo). There were no serious adverse events and treatment was well tolerated. After administration, rapid absorption led to peak plasmatic apomorphine concentrations at 1-2.6 min. Dose proportionality was observed for area under the curve and peak concentrations.

These results suggest that inhaled apomorphine may be well tolerated. On the other hand, interpretation of efficacy data is difficult due to a number of limitations, including limited sample size or lack of titration to optimal dose level. Indeed, peak apomorphine concentrations after 0.5 or 0.8 mg of the inhaled formulation were comparable to those attained after 1.6 mg doses of the subcutaneous formulation. Further studies evaluating higher doses are thus warranted.

Conflict of interests: SPLL has consulted for UCB France and for Neurohealing Pharmaceuticals Inc.

References.

1. Antonini A, Odin P. Pros and cons of apomorphine and L-dopa continuous infusion in advanced Parkinson's disease. *Parkinsonism Relat Disord* 2009;**15 Suppl 4**:S97-100.
2. Menon R, Stacy M. Apomorphine in the treatment of Parkinson's disease. *Expert Opin Pharmacother* 2007;**8**:1941-1950.
3. Lees A, Turner K. Apomorphine for Parkinson's Disease. *Practical Neurology* 2002;**2**:280-286.

4. Gunzler SA. Apomorphine in the treatment of Parkinson disease and other movement disorders. *Expert Opin Pharmacother* 2009;**10**:1027-1038.
5. Gershanik O, Jenner P. Moving from continuous dopaminergic stimulation to continuous drug delivery in the treatment of Parkinson's disease. *Eur J Neurol* 2012;**19**:1502-1508.
6. Perez-Lloret S, Rey MV, Fabre N et al. Prevalence and pharmacological factors associated with impulse-control disorder symptoms in patients with Parkinson disease. *Clin Neuropharmacol* 2012;**35**:261-265.
7. Grosset K, Malek N, Morgan F, Grosset D. Phase IIa randomized double-blind, placebo-controlled, study of inhaled apomorphine as acute challenge for rescuing 'off' periods in patients with established Parkinson's disease. *Eur J Neurol* 2012;