

EDITORIAL

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

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 *et al.* in 1951 and then by Cotzias *et al.* in 1970 [3]. Subcutaneous injection of the drug displayed potent but short-lived 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 10-fold affinity for D1 and D2 receptors compared with dopamine [2]. It also has 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, the mean latency to motor response is about 11–13 min, and the duration of action is about 56–62 min [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 min after administration as compared with placebo [2]. Such effects were present 6 months after initial evaluation. The 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]. Dyskinesias may also be reduced after infusion [5], thus highlighting its utility in patients with late-stage PD 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 three out of six 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.

In this issue of *European Journal of Neurology*, Grosset *et al.* report the results of a proof-of-concept efficacy and safety study of single doses of a recently developed inhaled apomorphine formulation [7]. Twenty-four patients with PD 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, 0.5 or 0.8 mg doses. However, there was a suggestion of benefit at the higher doses (five out of 12 patients switched 'on' at the 0.5 or 0.8 mg doses, versus one out of six 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 interest

SPLL has consulted for UCB France and for Neurohealing Pharmaceuticals Inc.

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