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Inhaled levodopa to abort off episodes in Parkinson's disease: concerns with dosage and effect sizes

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Oral levodopa combined with a DOPA decarboxylase inhibitor (DDI) is the gold standard of Parkinson's disease therapy. However, within 5 years of starting treatment, around 50% of patients develop debilitating off episodes, during which motor and non-motor symptoms reappear. Addition of a dopamine agonist, a monoamine-oxidase B (MAO-B) inhibitor or a catechol-O-methyltransferase (COMT) inhibitor, partly reduces daily time spent off, but some patients remain disabled to a point justifying use of complex, aggressive, expensive, and inconvenient device-based therapies. There is therefore a need for safer, cheaper, and more potent and convenient treatments.

The mechanisms generating off periods induced by levodopa therapy involve a complex interplay between pharmacokinetic and pharmacodynamic factors, including erratic gastrointestinal emptying and fluctuations in plasma concentrations below or above a threshold governing clinical switches from off to on states.¹ A strategy to tackle off problems is to develop longer acting levodopa-DDI formulations or more constant modes of delivery than currently available, to maintain stable concentrations above the threshold to prevent the occurrence of off episodes². Another approach is to administer very rapidly acting agents on demand, as soon as off episodes occur, to exceed the threshold and abort the off state (such as subcutaneous injections of apomorphine).

Pulmonary inhalation of levodopa, by-passing the gastric emptying obstacle, should rapidly bring plasma concentrations above the threshold to switch patients on. CVT-301 is a novel levodopa inhalation powder formulated for pulmonary absorption that can be administered using a passive breath-actuated device. Results from a 4-week, phase 2 trial conducted in 86 patients with Parkinson's disease showed that CVT-301 (50 mg) decreased patients' disability as measured by the Unified Parkinson Disease

Rating Scale (UPDRS) by 7 units more than did placebo when inhaled during off episodes ($p<0.001$). CVT-301 also reduced the time spent off by 0.9 hour/day more than did placebo ($p<0.05$)³.

LeWitt and colleagues have now further explored the effects of CVT-301 60 mg and 84 mg in a 12-week, phase 3 trial in 339 patients with Parkinson's disease⁴. The findings, published in *The Lancet Neurology*, show that reductions in mean UPDRS score from baseline to 30 minutes post inhalation were significantly greater with both doses of CVT-301 compared with placebo, confirming some of the initial phase 2 findings at a longer follow-up and in a larger cohort. However, CVT-301 was not better than placebo, or the effect was smaller than anticipated on several important secondary efficacy outcomes. These results deserve discussion regarding the potential effectiveness of the drug in clinical practice, as clinical trials can overestimate efficacy due to their research settings⁵. Although CVT-301 was superior to placebo in reducing UPDRS scores after 30 minutes, the difference was only borderline at 20 minutes ($p=0.062$), while a faster benefit (about 10 minutes) was expected from previous phase 2 findings, and patients are anxious to switch on as quickly as possible. Higher doses might be necessary in some patients to provide a faster response.

The reduction in UPDRS scores at 30 min with CVT-301 compared with placebo, although significant, was also smaller (-3.9 units) than expected from previous phase 2 results (-7 units). This finding is surprising, knowing the robust effect of levodopa, and considering the strong dopaminergic responsiveness of this cohort, illustrated by a mean baseline UPDRS score of about 35 in off and 16 in on periods, that is, a 19 unit difference. The authors argue that the patients might have inhaled the drug while not being fully off, which is a possibility. It is also conceivable that the tested doses might not have been high enough to provide a full response in all patients.

Surprisingly, there was no difference between CVT-301 and placebo in reducing the total time the patients spent in the off condition on a daily basis, even at 84 mg (-0.47 hours versus -0.48 hours). This is a concern, as diaries are the most straightforward, validated method to measure the impact of a treatment on off episodes over the day⁶. The minimal clinically significant difference in reducing time spent off is about 1 hour/day⁷. Interventions marketed to treat motor fluctuations have consistently

achieved this goal⁸. How then could CVT-301 have no impact on such outcome? The chances that higher CVT-301 doses than those used in this trial could exhibit a more robust effect on this outcome are plausible, and incomplete acute responses induced by insufficient doses might not have been captured with diaries. Perhaps the statistical power of the study was also insufficient, since previous trials that documented the efficacy of other interventions on this endpoint generally enrolled 150-200 patients per arm. However, one would have expected at least a trend in favour of CVT-301 in this trial, which was not the case. Intriguingly, CVT-301 50mg was superior to placebo on daily time spent off in the previously mentioned smaller phase 2 trial (45 patients per arm)³. Another possible reason for this negative result is that patients were not allowed to use CVT-301 before the first morning oral levodopa-DDI dose. Many patients wake-up in the off condition and have to wait up to 60 minutes or more before feeling the beneficial effects of their first oral levodopa-DDI dose. Inhaling CVT-301 at this moment seems then appealing. Unfortunately, CVT-301 does not contain a DDI, and DDIs have short plasma elimination half-lives⁹. It is therefore likely that decarboxylation might not be sufficiently blocked in the morning, after a night of levodopa-DDI withdrawal, to prevent the production of dopamine from CVT-301 at the periphery, with the risk of reduced efficacy and more gastrointestinal and cardiovascular adverse reactions. Furthermore, as pointed out by the authors, patients did not use CVT-301 during the day as much as they could have done, as they inhaled it on average twice a day only, while they had a mean of three or more off episodes per day. This limited usage might have also reduced the chances of CVT-301 producing a larger decrease in daily time spent off.

Trials also tend to underestimate adverse reactions. Patients with severe dyskinesia were excluded from this study and only around 40% of participants reported dyskinesia at baseline, while dyskinetic patients are at greater risk of worsening dyskinesia on dopaminergic supplementation. Longer and larger follow-up is also required before excluding pulmonary safety concerns regarding inhaled levodopa, especially in patients with lung co-morbidities.

In summary, the present trial is a welcome addition, as the principle of inhaling levodopa is appealing and findings provide evidence that CVT-301 improves symptoms of Parkinson's disease. However, the effect sizes recorded in this trial are not as good as anticipated, in terms of speed and amplitude of the acute response

and of impact on daily time spent off. Some patients may require higher doses than 84 mg to fully switch on, and this should be investigated, if technically possible with this device. Post-hoc analyses of off time responders rather than “UPDRS responders might facilitate understanding of the specific target population. Moreover, CVT-301 should be compared with apomorphine subcutaneous injections, which significantly improve UPDRS scores by 10-20 units within 20 minutes after administration¹⁰⁻¹². Inhaling a drug is more convenient than using a penjet. Inhaled and sublingual apomorphine formulations are also under development for that reason^{13,14}.

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