Profile of Inhaled Levodopa and its Potential in the Treatment of Parkinson's Disease:

Evidence to Date

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Introduction:

Levodopa has been the gold standard for the treatment of Parkinson's disease since the 1960s. However, it has been associated with both short-term (e.g., nausea, hypotension, hallucinations) and long-term side effects (e.g., motor fluctuations and dyskinesias).

- **Motor fluctuations**: Motor symptoms experienced during On and Off times experienced by PD patients which correlate with higher and lower levodopa concentrations.
    - Can become more disabling than primary motor symptoms of PD
    - 50-60% of patients starting Levodopa will develop motor complications within 3-4 years

There are various factors that contribute to the lack of consistent dopamine stimulation when using Levodopa:

- Levodopa has a short half-life (the time period when the medication becomes significantly less effective; 0.7-1.4 hours) and time to maximum plasma concentration (15-60 minutes).
- Delayed gastric emptying, competition with other proteins in one's diet for transport from the gut to the bloodstream and competition for transport across the blood-brain barrier.
- Desensitization within the receptors in the brain.

Several adjunctive medications (e.g. Dopamine agonists with longer half-lives, Injectable short-acting dopamine agonists, antidyskinetic agent) have therefore been used to address the motor complications from Levodopa use. This article reviewed the effectiveness and safety of a novel dry-powder aerosol self-administered inhaled levodopa formulation (CVT301) for use in treating Off episodes of PD.

D**eveloping Levodopa formulations:**

Newer formulations are being developed to compensate for the various side effects of oral Levodopa use to enhance more continuous dopamine stimulation in the brain. Two novel formulations of levodopa currently under development include a combination of carbidopa/levodopa and have been designed to increase gastric retention of the drug (retention of the drug in the stomach) or provide constant levodopa concentration with the use of a belt-pump or patch-pump system.

Inhaled levodopa (CVT301)

- Inhaled dry-powder formulation of levodopa with an inhalation device where patients can self-administer the medication by breathing in.
- Developed with the goal of producing rapid, consistent increases in drug concentrations with rapid clinical response.

1. <u>Preclinical phase – Animal studies</u>
    a. Inhaled levodopa was associated with faster time to maximum plasma concentration (2 minutes vs. 15-20 minutes)
    b. Tenfold difference in the dose of drug required to produce equivalent peak benefit.

c. No abnormalities in lung tissue.
d. Pulmonary delivery resulted in more rapid and less variable absorption.

2. Clinical Development: Phase I – Healthy human studies (18 males, aged 30-65)
    a. All inhaled doses led to a more rapid increase in plasma levodopa concentrations.
    b. Less variability in plasma levodopa concentrations.
    c. 4 adverse events: dizziness (2), headache and muscle spasm.

3. **Clinical Development: Phase II (A&B)– Idiopathic PD (diagnosed at ages 30-80)**
    a. **The study concluded that the inhaled levodopa delivery was safe, well tolerated and led to rapid and more consistent levodopa absorption compared to oral levodopa in the Off state.**
    b. **It was also associated with more rapid improvement in motor function following individual doses.**

4. Clinical Development: Phase III – PD patients with motor fluctuations
    a. This study confirmed that there is clinically meaningful response to inhaled levodopa in reduction of motor symptoms and that the drug is safe and tolerable.
    b. Primary adverse events included mild cough, upper respiratory tract infection, nausea, saliva discoloration and dyskinesia.

5. Long-term and other safety studies
    a. Two studies suggested that long-term use of inhaled levodopa is effective in treating Off episodes and does not alter the natural progression of breathing functions.
    b. Other studies done on special populations (e.g., asthmatics, smokers) concluded that the drug was safe and tolerated with the most common adverse effect being cough.

Conclusion & Potential for inhaled Levodopa in treatment of PD

- Investigators are currently working on developing an improved inhaler device, which could make use of the drug easier for PD patients during their Off periods.
- Evidence to date does not support the use of inhaled Levodopa for primary treatment of PD.
- However, it could be used as an alternative rescue therapy to reduce Off times, with several advantages (easy to self-administer, well-tolerated, reliably achieves On-state).
- A new-drug application for CVT301 under the brand name Inbrija was filed in February 2018, for use as needed during Off periods.

Summary of CVT301 (inhaled levodopa)

- Leads to rapid rise in plasma levodopa concentration with onset of effect within 5-10 minutes, peak effect at 30 minutes.
- In most studies, transition from Off to On periods do not lead to dyskinesias.
- Overall, the drug was considered safe and well tolerated across studies.
- CVT301 demonstrated effective rescue therapy for management of Off symptoms.