CONSTANT STEADY-STATE PLASMA CONCENTRATIONS OF LEVODOPA FOLLOWING SUBCUTANEOUS ADMINISTRATION OF LEVODOPA AND CARBIDOPA: A NOVEL THERAPEUTIC APPROACH

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Background

The most common problems of advanced Parkinson's disease (PD) – wearing-off between doses and dyskinesias – are linked to the marked fluctuations of circulating levodopa (LD) that typically occur during oral administration of all available products. The brief absorption and clearance half-life of LD create the pharmacological challenge for improving plasma LD pharmacokinetics (PK). Currently-available long-acting oral LD therapies usually fail at controlling variability in motor control of PD. In contrast, marked clinical improvements (reduced dyskinesias and "off" periods) can be achieved from LD treatment by continuous intravenous or intraduodenal infusion. However, neither of these invasive drug delivery options is practical for most patients. For this reason, Neuroderm investigated the effects of continuous subcutaneous delivery of a LD/carbidopa (CD) formulation, ND0612, a promising alternative means for maintaining steady levodopa levels and improved bioavailability of levodopa.

Objective

To determine the pharmacokinetic (PK) profile of LD following continuous subcutaneous (SC) administration of solubilized forms of carbidopa (CD) and LD.

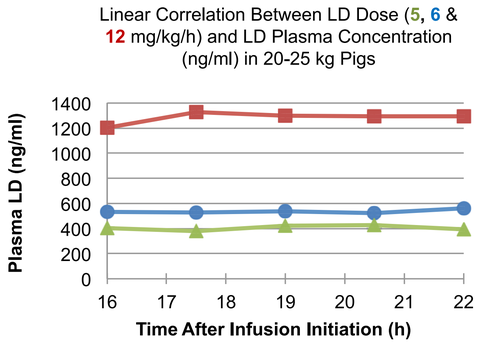
Methods

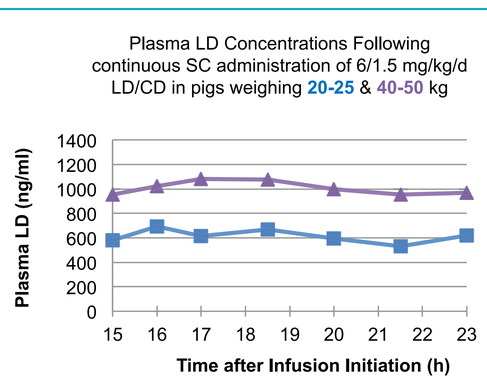
We developed a novel method for solubilizing and stabilizing LD and CD for use in continuous SC administration of a LD/CD mixture. Domestic pigs (weighing either 24±4 kg or 41±4 kg) received continuous SC administration of LD/CD. Several concentrations and rates of delivery were accomplished with an insulin pump running continuously for periods of 24-46 hrs. Venous blood samples were collected at pre-determined time points, and plasma concentrations of LD and CD were measured using high-performance liquid chromatography with electrochemical detection.

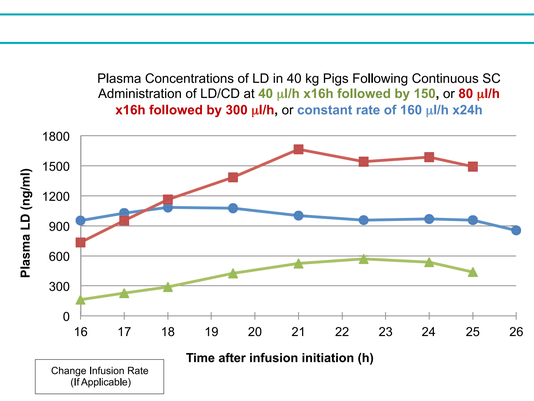
Results

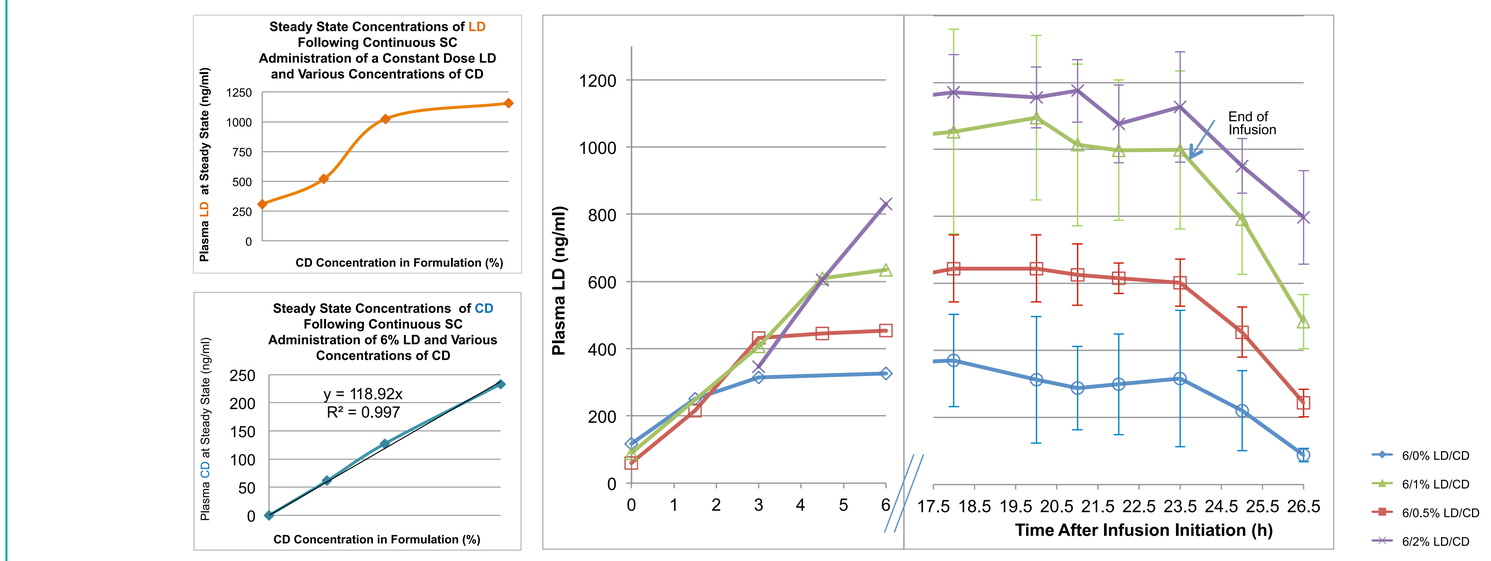
Constant plasma LD concentrations were maintained following continuous SC administration of LD/CD formulations in pigs.

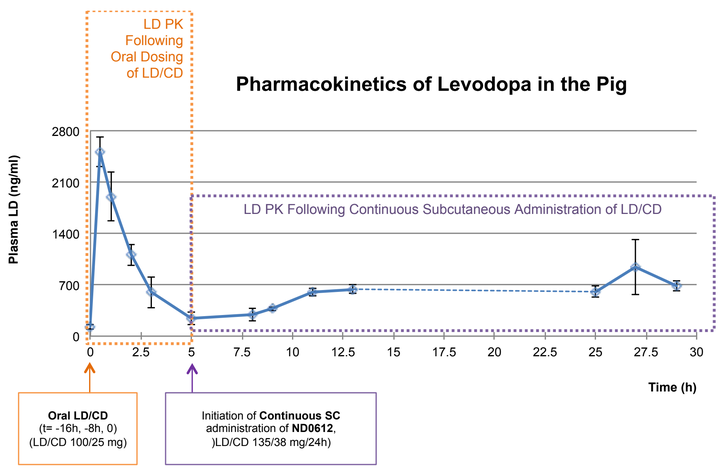
- The steady-state plasma concentrations of LD were dose-dependent on rates of infusion for both LD and CD.
- The time to reach steady state concentration of LD was about 6 hours.
- No troughs in LD concentration were observed following pump replacement.
- Continuous SC delivery of ND0612, 2-4 ml/d, was sufficient to obtain and maintain constant LD plasma concentrations at a range that typically produces an anti-Parkinsonian effect in PD patients.
- The treatment was safe and well tolerated.

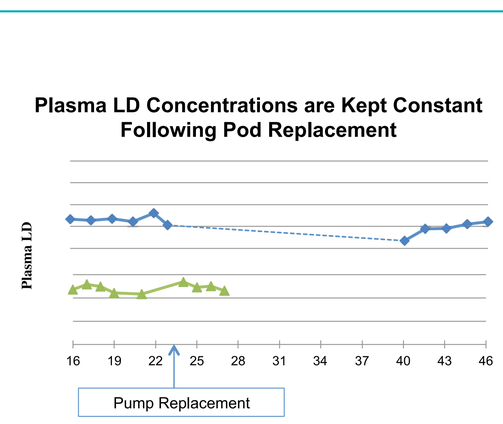












Conclusions

Currently-available oral LD formulations are associated with marked PK fluctuations. SC delivery of solubilized LD and CD is a promising option for enhancing consistency of plasma LD concentrations. ND0612 is being developed for administration as an adjunct to oral levodopa via a subcutaneous delivery patch as a new treatment and intervention option in Parkinson's disease treatment. It should reduce off-time and improve the management of motor fluctuations and reduce the burden of frequent daily oral dosing with LD/CD

A clinical trial evaluating safety, tolerability and PK profile of plasma LD following continuous SC administration of LD/CD is ongoing. The study is a single center, double-blind, randomized, placebo-controlled, phase I, dose escalating study. 6 healthy volunteers will be dosed in each treatment group in a sequential manner. Subject will be administered subcutaneous (SC), at two sites, ND0612 (LD/CD solution) and placebo (saline), in parallel, in a double blind manner. Plasma concentration of levodopa and carbidopa will be determined.