MAINTENANCE OF CONSTANT STEADY STATE THERAPEUTIC PLASMA CONCENTRATIONS OF LEVODOPA FOLLOWING ITS CONTINUOUS SUBCUTANEOUS ADMINISTRATION WITH CARBIDOPA

O. Yacoby-Zeevi[1] and P. A. LeWitt[2], [1]NeuroDerm, Ltd, Ness Ziona, Israel [2]Neurology, Wayne State University School of Medicine and Henry Ford Hospital, West Bloomfield, MI, USA.

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. 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 often 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 drug delivery options is convenient. For this reason, we investigated the effect of continuous subcutaneous delivery of LD/CD formulations, ND0612, on the PK of LD.

Objectives

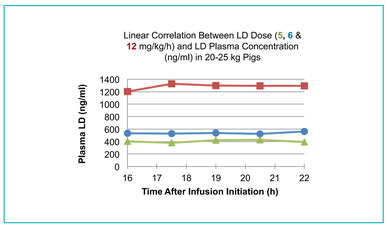
To test the effect of continuous subcutaneous (SC) administration of ND0612 (a LD/CD formulation) on the PK of LD

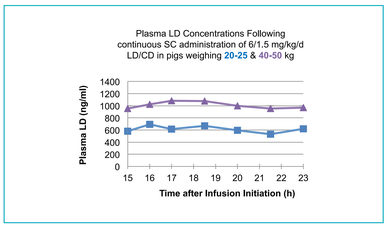
Materials and Methods

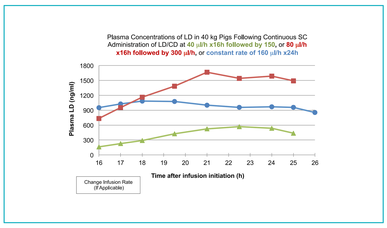
A novel method for solubilizing and stabilizing LD and CD was developed and used to carry out continuous SC administration of LD/CD in pigs. Domestic pigs weighing either 24±4 kg or 41±4 kg were continuously administered SC with LD/CD at several concentrations and rates via an insulin pump for periods between 24-46 hrs. Venous blood samples were collected at pre-determined time points and plasma LD and CD concentrations were measured using HPLC-ECD.

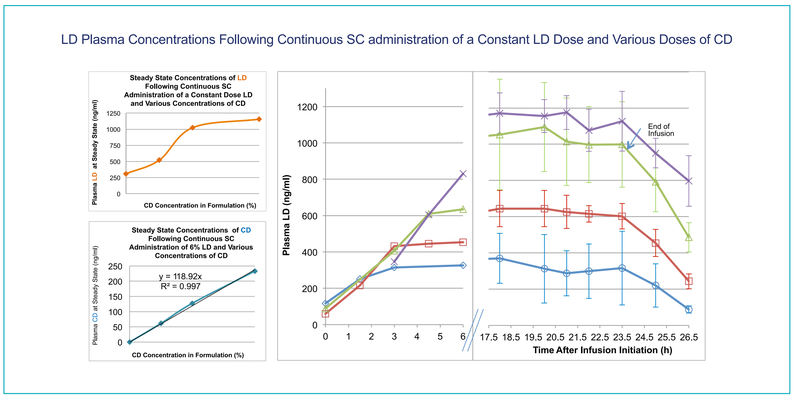
Results

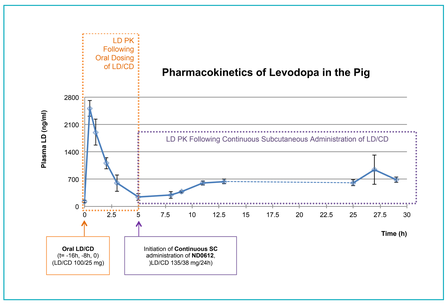
- Constant plasma LD concentrations were maintained following continuous SC administration of LD/CD formulations in pigs.
- The LD steady state plasma concentrations were both LD and CD dose-dependent.
- The time to reach steady state concentration was about 6 hours, but no troughs were observed following pump replacement.
- Continuous SC delivery of ND0612, 2-4 ml/d, was sufficient to obtain and maintain constant LD plasma concentrations at a range typically therapeutic for treating PD.
- The treatment was safe and well tolerated.

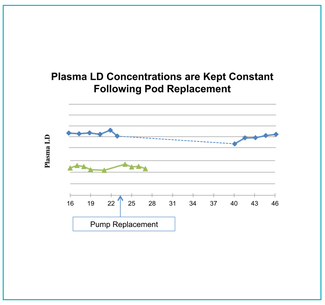












Conclusions

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. This approach offers improved control of motor fluctuations in advanced PD and an opportunity to reduce the burden of frequent daily oral dosing with LD/CD

A Phase I randomized, cross-over, double-blind, placebo-controlled study evaluating safety, tolerability and PK profile of plasma LD following continuous SC administration of LD/CD is ongoing.