Pharmacokinetic analysis of levodopa and carbidopa following subcutaneous infusion: A population pharmacokinetics model

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Introduction & Objectives

- ND0612 is an investigational subcutaneous delivery system providing minimally invasive, continuous infusion of liquid levodopa/carbidopa. By avoiding gastric involvement, ND0612 provides increased bioavailability and reduced variability of levodopa/carbidopa plasma levels, potentially offering more reliable, sustained relief of motor fluctuations in people with Parkinson's disease.
- Several pharmacokinetic (PK) studies have been performed and have confirmed stable, clinically relevant levodopa and carbidopa plasma levels following ND0612 administration.[1-4]
- Here we describe the development of a model to describe the PK characteristics of levodopa and carbidopa following subcutaneous infusion with ND0612, with and without oral therapy, including associated interindividual variability and residual unexplained variability.

Methods

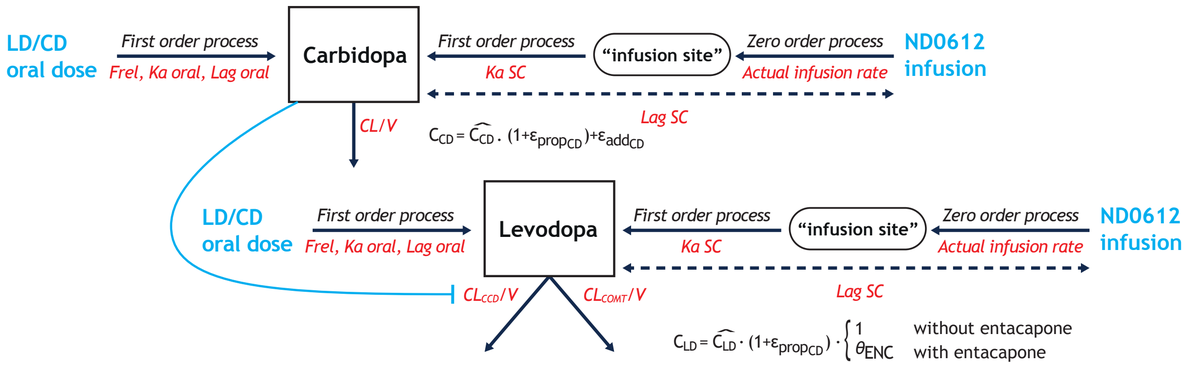
- Two integrated population PK models (for levodopa and for carbidopa) were developed using data from two Phase I studies of ND0612 in healthy volunteers and PD patients.
  1. Study 004, a randomized, multicenter, dose finding study including 16 PD patients on active treatment (n=1438 PK observations).[2]
  2. Study 005, including 36 healthy volunteers on active treatment (n=3417 PK observations).[3]
- The predictive performance of each model was then tested using data from Study 114, which included 24 healthy volunteers on active treatment (n=2959 PK observations).[4]
- Model refinement was performed using aggregated data from the 3 studies, and will be continually updated as more PK data from ND0612 studies becomes available.
- Population PK models were developed by using non-linear mixed-effects modeling techniques as implemented in the NONMEM 7.3 software.

Conclusions

- Both levodopa and carbidopa follow a one-compartment PK with first-order oral and SC absorption.
- The levodopa population PK model also takes into account DDC and COMT elimination from the central compartment.
- Structural covariates include body weight and entacapone coadministration.
- Apparent clearance and volume of distribution decrease with increasing age for both compounds.

Results

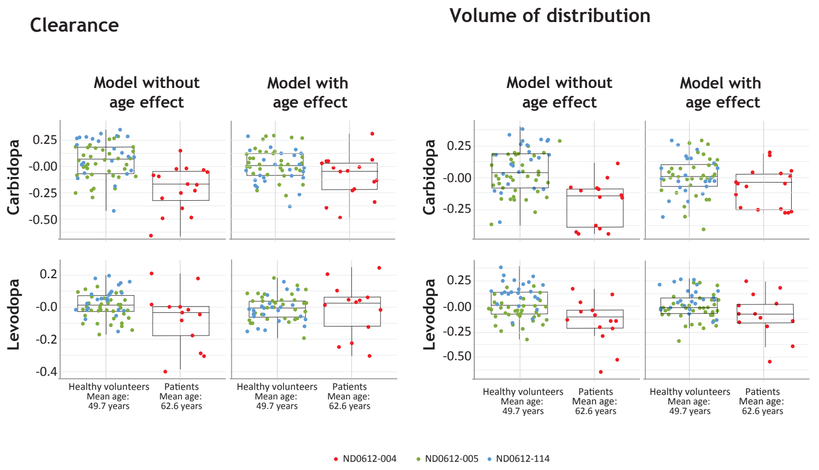
Levodopa and carbidopa population PK were both adequately described by a one-compartment disposition model with first-order oral and SC absorption.



- Levodopa had parallel DDC and COMT elimination from the central compartment, in which the inhibition of apparent DDC-mediated levodopa clearance for SC administration was inhibited by carbidopa.
- Carbidopa had linear elimination.
- Exploration of covariates revealed that age had a significant effect on apparent clearance and apparent volume of distribution for both carbidopa and levodopa, even after accounting for body weight differences; both parameters decreased with increasing age.

Exploratory models for CD and LD (developed based on data from studies ND0612-004 and ND0612-005 only). The blue line indicates inhibition of the LD DDC levodopa elimination pathway by carbidopa systemic concentrations. CL: clearance, C_{CD}: measured CD concentration $\widehat{C_{CD}}$: predicted CD concentration, C_{LD}: measured LD concentration, $\widehat{C_{LD}}$: predicted LD concentration, CL_{DDC}: DDC-mediated CL, CL_{COMT}: COMT-mediated CL, $\varepsilon_{add_{CD}} \sim N(0,\sigma^2_{add_{CD}})$, $\varepsilon_{prop_{CD}} \sim N(0,\sigma^2_{prop_{CD}})$, $\varepsilon_{prop_{LD}}(0,\sigma^2_{LD})$, Frel: relative bioavailability between oral and SC administration, Ka: first-order absorption rate constant, θ_{ENC}: relative LD bioavailability with entacapone, Lag: lag time, SC: subcutaneous, V: volume of distribution.

Apparent clearance and volume of distribution decreases with increasing age for both compounds.



References

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Disclosures

Pharmetheus (MB, GS, NJ and MK) provided consultancy to NeuroDerm. Liat Adar, Tal Birnberg, Ryan Case are employed by NeuroDerm, Sheila Oren was employed by NeuroDerm at the time of study. Assistance for this poster was provided by A. White and A. Patel (funded by NeuroDerm).

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