Pharmacokinetic analysis of levodopa and carbidopa following subcutaneous infusion: A population pharmacokinetic-pharmacodynamic model

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Objective: To describe the population pharmacokinetics (PK) of levodopa and carbidopa following subcutaneous infusion with and without oral therapy, including associated interindividual variability and residual unexplained variability.

Background: ND0612 is in development as the first drug-device combination delivering liquid levodopa/carbidopa via continuous subcutaneous (SC) infusion to reduce motor complications in patients with Parkinson's disease (PD). Several PK studies have been performed and have confirmed stable levodopa and carbidopa plasma levels following ND0612 administration.

Methods: Two separate population PK models (for levodopa and for carbidopa) were developed using data from two Phase I studies of ND0612 (Studies 004 and 005), accounting for combined zero- and first-order absorption processes (representing SC infusion and oral + SC absorption, respectively). The predictive performance of each model was then tested using data from a third study (Study 114). 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.

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 dopa decarboxylase (DDC) and COMT elimination from the central compartment, in which the inhibition of apparent DDC-mediated levodopa clearance for SC administration was driven by plasma concentrations. Carbidopa had linear elimination. Covariates exploration revealed that age had a statistically significant effect on apparent clearance and apparent volume of distribution for both carbidopa and levodopa, with the two parameters decreasing with increasing age.

Conclusions: Model diagnostics for the carbidopa and levodopa population PK models indicated a satisfactory predictive performance, supporting their usability to derive individual predictions of exposure to be used in future pharmacokinetic-pharmacodynamic analyses.

Introduction & Objectives

- ND0612 is in development as the first drug-device combination delivering liquid levodopa/carbidopa via continuous subcutaneous (SC) infusion to allow for continuous plasma levodopa/carbidopa delivery to reduce motor complications in patients with Parkinson's disease (PD).
- 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, including associated interindividual variability effects of patients characteristics.

Methods

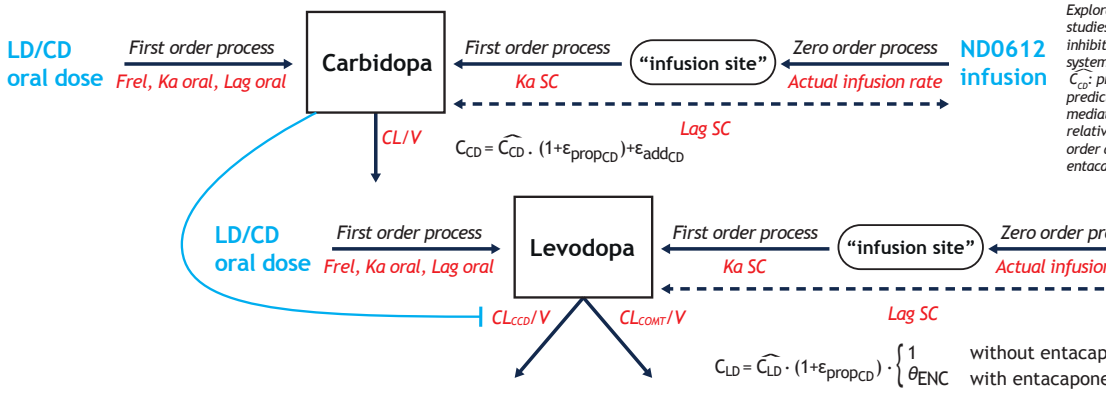
- Two separate population PK models (for levodopa and for carbidopa) were developed using data from two Phase I studies of ND0612.
  1. Study 004, a randomized, multicenter, dose finding study including 16 PD patients on active treatment (n=1438 PK observations).[2]
  2. Study 005, including 36 healthy 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

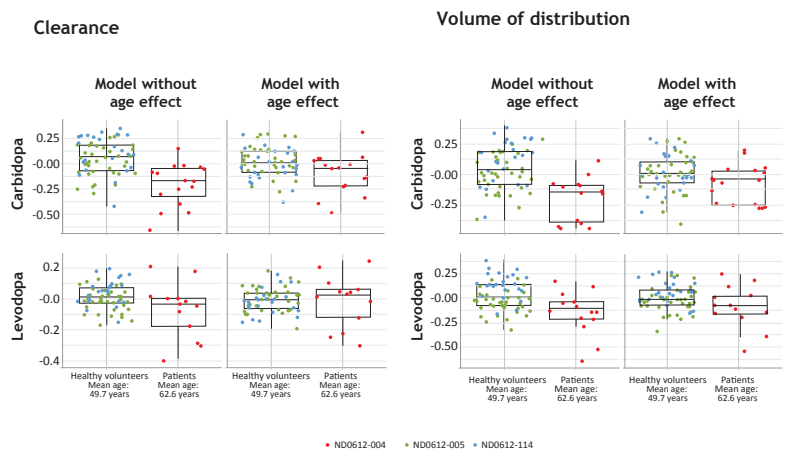
Levodopa and carbidopa population PK were both adequately described by a one-compartment disposition model with first-order oral and SC absorption.



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.

- 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.
- Body weight was included as a structural covariate on the disposition parameters of both compounds based on allometry; entacapone coadministration was also a structural covariate on levodopa oral/SC bioavailability.

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



References

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2. Adar et al. Neurology 2017; 88 (S16): P1.019.
3. Adar et al. Mov Disord. 2017; 32 (S2).
4. Birnberg et al. Mov Disord Clin Pract 2020; 7(S1): S37.

Disclosures

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