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

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Introduction & Objectives

ND0612 is in development as the first drug-device combination delivering 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 DDC (dihydroxyphenylalanine) and COMT (catechol-O-methyltransferase) elimination from the central compartment, in which 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 levodopa and carbidopa, 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 utility to derive individual predictions of exposure to be used in future pharmacokinetic-pharmacodynamic analyses.

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.

References

3. Adar et al. Mov Disord. 2017; 32 (S2).

Disclosures

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