ND0611 ADMINISTRATION OF CONTINUOUS SUBCUTANEOUS CARBIDOPA IMPROVES LEVODOPA PHARMACOKINETICS

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Background
Two common problems of advanced Parkinson's disease (wearing-off between doses and peak-effect dyskinesias) correlate to the marked fluctuations of circulating levodopa (LD) occurring typically during oral administration. Ways for improved consistency of plasma LD concentrations have been a longstanding pharmacological challenge. Initially, we found in our experiments that, despite continuous administration of LD, its plasma pharmacokinetics (PK) nonetheless showed a pulsatile pattern linked to the timing of oral carbamidopa (CD) dosing. With the hypothesis that CD interacts with LD uptake or its clearance (or both), we investigated the effect of continuous systemic delivery of CD (ND0611) on LD pharmacokinetics.

Materials and Methods
A novel method for solubilizing CD was developed and used for testing continuous systemic administration of CD (60 mg/24 hours) in pigs (ND0611) with standardized regimens of Sinemet®, Sinemet CR® and Stalevo® co-administered orally. Plasma LD concentrations were measured repeatedly for PK analysis.

Study Design
Pigs (~35 kg) were equipped with patches delivering LD at 60 mg/24 hours. They received one of three marketed LD formulations administered orally (immediate-release Sinemet®, Sinemet CR®, or Stalevo®) q8h or q12h. Plasma specimens were sampled at regular intervals for pharmacokinetic analysis of LD, 3-O-methyldopa (3-OMD), and CD concentrations.

Results
To test the effect of continuous parenteral CD (ND0611) administration on LD PK, following oral administration of three marketed LD formulations.

Objective
Continuous administration of CD increased the half-life of LD and reduced the fluctuation of LD concentrations in plasma compared to the oral administration.

Conclusions
Intermittent oral CD dosing contributes to fluctuations in LD pharmacokinetics. Continuous subcutaneous delivery of ND0611 that was administered in addition to oral intake of LD did not duplicate the effect of giving this drug subcutaneously. The mechanism for these observations is not immediately apparent, but one possibility for the altered LD pharmacokinetics is shown in the following diagram:

A Phase III single-center, randomized, crossover, double-blind, placebo-controlled study is ongoing evaluating safety, tolerability, and pharmacokinetic profile of LD following continuous subcutaneous administration of ND0611; this study involves a comparison to oral administration of marketed LD formulations in LD-treated Parkinson’s disease patients experiencing motor fluctuations and dose-by-dose LD effects.

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