ND0611 ADMINISTRATION OF CONTINUOUS SUBCUTANEOUS CARBIDOPA IMPROVES LEVODOPA PHARMACOKINETICS

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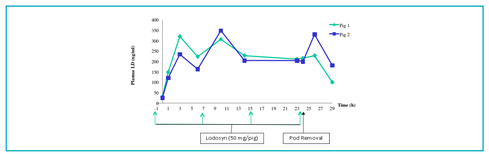
Background

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 carbidopa (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.

Fluctuations in Plasma Levodopa Concentrations , Despite Continuous Subcutaneous Administration of Levodopa-Ester, Coincided with Oral Administration of Carbidopa in the Pig



Objectives

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

Materials and Methods

A novel method for solubilizing CD was developed and used for testing continuous 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

Pig study

Pigs (~35 kg) were equipped with patches delivering CD at 60 mg/24 hours

They received one of 3 marketed LD formulations administered orally (immediate-release Sinemet©, Sinemet CR©, or Stalevo©) q8 or q12hr

Plasma specimens were sampled at regular intervals for pharmacokinetic analysis of LD, 3-O-methyldopa (3-OMD), and CD concentrations

Mouse study

Alzet© osmotic pumps with ND0611 or its vehicle were implanted SC in mice

LD/CD was administered orally x 4, q8h

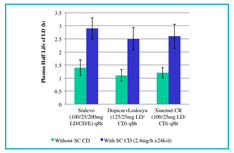
After the last oral dosing blood and brain were collected at pre-determined time-points (n=3/treatment/ time point)

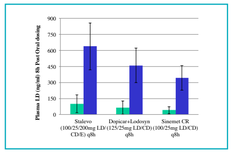
LD, CD and 3-OMD concentrations were measured in plasma; LD and dopamine were quantified in brain

Results

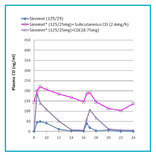
Pig study

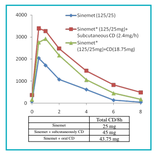
ND0611 Significantly Increased the Half-Life (h) and Trough Concentrations of levodopa (ng/ml), 8h Post-Oral Dosing of Levodopa/CD in the Pig

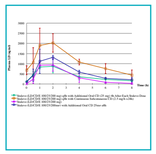




The Effect of ND0611 on the Pharmacokinetic of Levodopa Could Not be Duplicated by Increasing Oral Intake of CD







The Effect of ND0611 on the Pharmacokinetics of Levodopa in the Pig

Supplemental Carbidopa	Stalevo (100/25/200 mg)				
	C_{max}	T_{max}	$T_{1/2}$	AUC_{0-t}	$AUC_{0-\infty}$
None	2392 ±1363.9	2.3 ±0.89	1.4 ±0.30	8109 ±4145.2	8309 ±4265.2
Subcutaneous ND0611, 60mg/d	2355 ±1157.1	2.1 ±1.00	2.9 ±0.41	17527 ±8470.8	19330 ±8284.8
Oral CD 18.75mg x3/d	1643 ±349.7	3.8 ±1.67	1.5 ±0.47	9774 ±3928.7	10218 ±3955.5

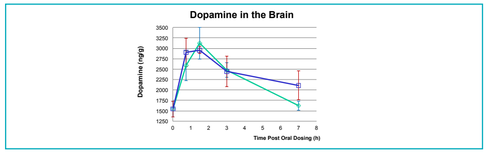
Supplemental Carbidopa	Levodopa/CD (125/25 mg)				
	C_{max}	T_{max}	$T_{1/2}$	AUC_{0-t}	$AUC_{0-\infty}$
None	2472 ±735.6	0.9 ±0.53	1.1 ±0.22	7200 ±3093.2	7302 ±3071.3
Subcutaneous ND0611, 60mg/d	4050 ±1369.5	0.8 ±0.43	2.5 ±0.43	17922 ±4375.7	19230 ±4625.5
Oral CD 18.75mg x3/d	3445 ±943.2	0.9 ±0.52	1.6 ±0.16	11994 ±2749.0	12267 ±2757.6

Supplemental Carbidopa	Sinemet CR (100/25 mg)				
	C_{max}	T_{max}	$T_{1/2}$	AUC_{0-t}	$AUC_{0-\infty}$
None	1691 ±556.2	0.9 ±0.52	1.2 ±0.19	4792 ±1190.8	4929 ±1196.6
Subcutaneous ND0611, 60mg/d	2830 ±929.2	1.2 ±0.92	2.6 ±0.46	12688 ±3516.3	13505 ±3344.4

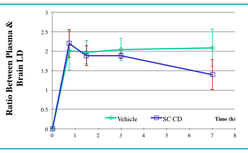
Much less fluctuation in plasma LD concentration was observed when CD was infused subcutaneously, in addition to its oral intake. The LD area-under-the-concentration-curve vs. time, clearance half-life, and trough concentrations were substantially increased with the CD infusions. Oral intake of CD given in comparable dosage did not duplicate the effect of giving this drug subcutaneously.

Mouse study

Continuous SC Administration of CD Increased the Half-life of Dopamine in the Brains of Mice



The Ratio Between Plasma and Brain Levodopa-Concentration was Reduced when Continuous Subcutaneous CD was Co-administered with Oral CD/levodopa



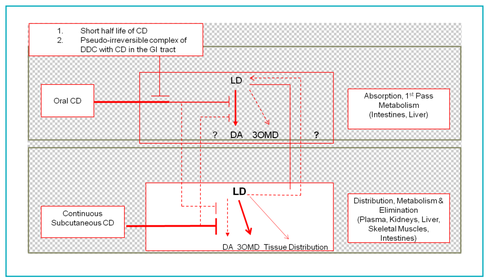
Conclusions

Intermittent oral CD dosing contributes to fluctuations in LD pharmacokinetics.

Continuous subcutaneous delivery of ND0611 offers a promising option for enhancing consistency of plasma LD concentrations and, thus, the effect of LD in improving the treatment of motor fluctuations and dyskinesias in Parkinson's disease.

Practical applications of these findings might be improved control of motor fluctuations in Parkinson's disease, and the opportunity to reduce the frequency needed for repeated LD doses.

The mechanism for this these observations is not immediately apparent, but one possibility for the altered LD pharmacokinetics is shown in the following diagram:



A Phase I/II 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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