ND0611 Markedly Enhanced Levodopa Pharmacokinetics from Continuous Subcutaneous Carbidopa Administration

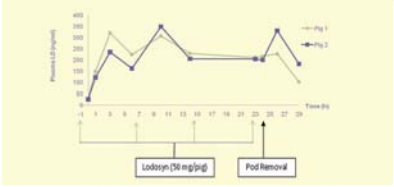
O. Yacoby-Zeevi[1], S. Oren[1], and P. LeWitt[2]

[1]NeuroDerm, Ltd, Ness Ziona, Israel; [2] Department of Neurology, Henry Ford Hospital, West Bloomfield, Michigan, USA

Introduction

The most common problems of advanced Parkinson's disease – wearing-off between doses and dyskinesias – are linked to the marked fluctuations of circulating levodopa that typically occur during oral administration. Improving the consistency of plasma levodopa concentrations has been a longstanding pharmacological challenge. In our experiments, despite continuous administration of levodopa, its plasma pharmacokinetics nonetheless showed a pulsatile pattern, which correlated with the timing of oral carbidopa (CD) dosing. With the hypothesis that CD interacts with levodopa uptake and/or its clearance, we then planned investigations of levodopa pharmacokinetics during continuous systemic delivery of CD.

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 subcutaneous administration of CD (ND0611) on the pharmacokinetics of levodopa, following its oral administration using marketed oral levodopa formulations

Materials and Methods

ND0611, a novel formulation of solubilized CD was developed and used for the continuous subcutaneous administration of CD.

Study Design

Pig study

- Pigs (~35 kg) were equipped with patches delivering CD at 60 mg/24 hours
- They received one of 3 marketed levodopa formulations administered orally (immediate-release Sinemet©, Sinemet CR©, or Stalevo©) q8 or 12h.
- Plasma specimens were sampled at regular intervals for pharmacokinetic analysis of levodopa, 3-O-methyldopa, and CD

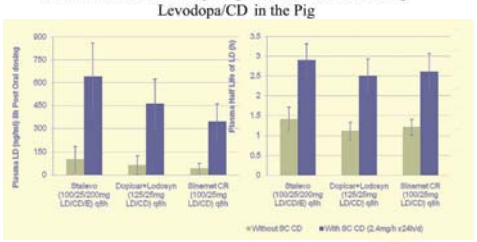
Mouse study

- Alzet osmotic pumps with ND0611 or its vehicle were implanted SC in mice
- Levodopa/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)
- Levodopa, CD and 3-O-methyldopa (3-OMD) were quantified in plasma; levodopa and dopamine were quantified in brain

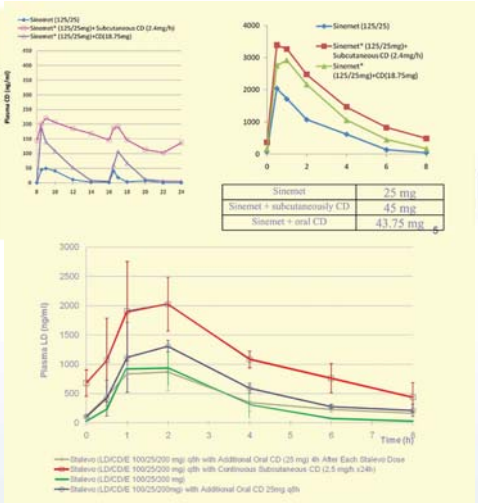
Results

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



Sinemet	25 mg
Sinemet + subcutaneously CD	45 mg
Sinemet + oral CD	43.75 mg

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 ×3/d	1643 ±349.7	3.8 ±1.67	1.5 ±0.47	9774 ±3928.7	10218 ±3955.5

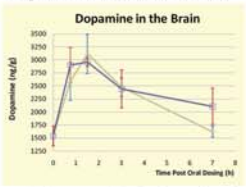
Supplemental Carbidopa	LD/CD (125/25 mg)				
	C_{max}	T_{max}	$T_{1/2}$	AUC_{0-t}	$AUC_{0-\infty}$
None	2472 ±735.6	0.9 ±0.53	1.1 ±0.22	7200 ±3093.2	7302 ±3071.3
Subcutaneous ND0611, 60mg/d	4050 ±1369.5	0.8 ±0.43	2.5 ±0.43	17922 ±4375.7	19230 ±4625.5
Oral CD 18.75mg ×3/d	3445 ±943.2	0.9 ±0.52	1.6 ±0.16	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

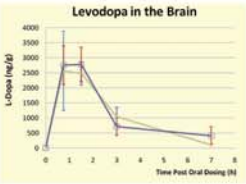
- Much less fluctuation in plasma levodopa concentration was observed when CD was infused subcutaneously.
- The levodopa area-under-the-concentration-curve vs. time, clearance half-life, and trough concentrations were substantially increased from the CD infusions.
- When given orally, CD did not duplicate the effect of subcutaneous administration.

Mouse study

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



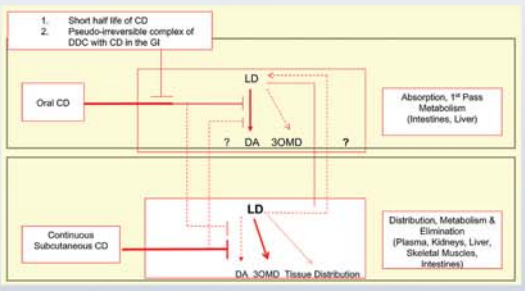
The Ratio Between Plasma *and* Brain Levodopa-Concentration was Reduced when Continuous Subcutaneous CD was Co-administered with Oral CD/levodopa



Conclusions

- Intermittent oral CD dosing contributes to fluctuations in levodopa pharmacokinetics.
- Continuous subcutaneous delivery of ND0611 offers the potential for improving the consistency of levodopa effect in treating Parkinson's disease.
- Practical applications might be improved control of motor fluctuations in Parkinson's disease, and the opportunity to reduce the frequency of repeated levodopa doses.

An explanation for how this strategy improves the pharmacokinetic profile of levodopa remains to be elucidated



LD: levodopa 3OMD: 3-O-methyldopa DDC: dopa decarboxylase

A Phase I clinical trial of subcutaneous administration of ND0611 in levodopa-treated young healthy human volunteers has been completed and analysis is ongoing.