Rapid uptake and stable serum levodopa levels with continuous s.c. Infudopa (levodopa/carbidopa) administration

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Levodopa/carbidopa (LD/CD) intestinal gel infusion has superior efficacy in advanced PD compared to oral treatment, but requires surgery and a permanent percutaneous gastrojejunostomy. Subcutaneous infusion therapy would be more accessible but the low solubility of levodopa at physiological pH has made this approach less feasible.
The phase I, open-label, randomized, crossover trial IPO-001 (NCT03419806) characterizes the pharmacokinetic properties and safety of Infudopa, a high concentration LD/CD solution which is buffered online during infusion.

Method

Intravenous and subcutaneous Infudopa is compared with Duodopa® in patients with advanced PD. Plasma levels of levodopa and carbidopa are analysed during a 16h infusion period and up to 24h after a morning bolus dose. Dosing was based on patients regular Duodopa® dose. In the first five patients the same composition was used both for i.v. and s.c. infusions. A modified composition (Infudopa SubC) is used for s.c. infusions in the remainder of the study and dosing is adjusted based on pharmacokinetic data from the first five patients. In total 23 patients are planned.

Results

First five patients (All male, age 58-76)

Table 1. Average and SD of levodopa doses in patients 1-5.

Variable	Levodopa
Mean (SD) s.c.	1759 (619) mg
Mean (SD) LCIG	1761 (622) mg
Mean (SD) i.v.	1321 (466) mg

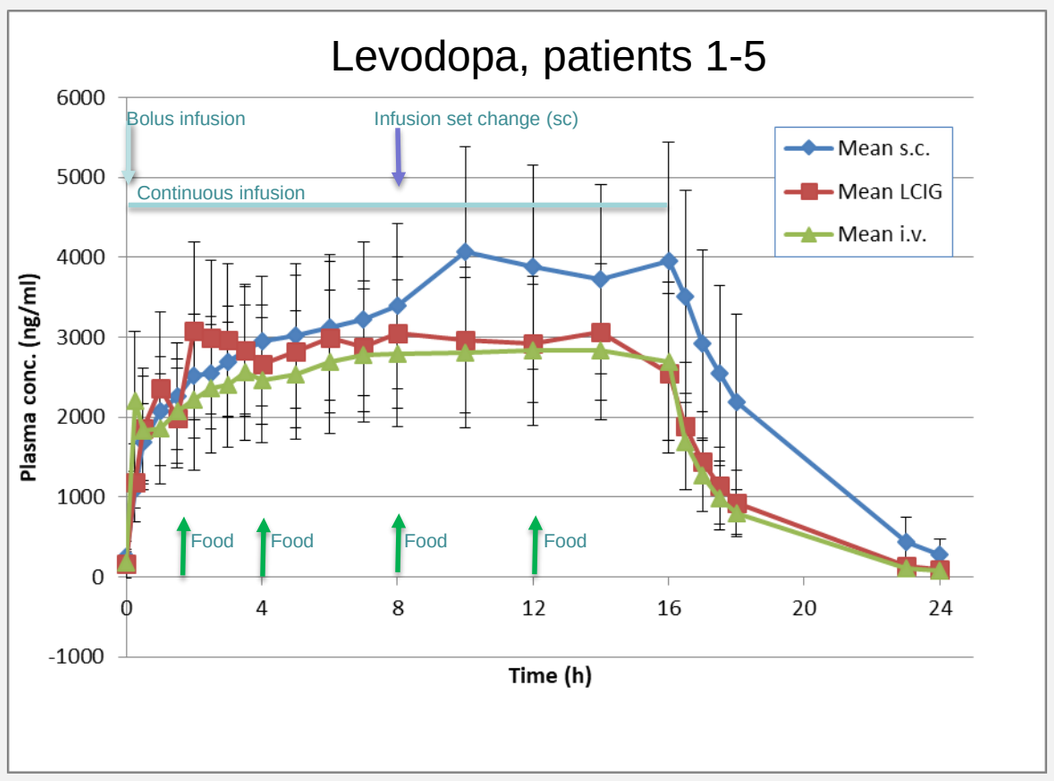

Figure 1. Plasma levels of levodopa during 16h infusion and up to 24h (mean±SD). Patients normal morning bolus was used and 75% of the LCIG dose was used for Infudopa i.v. treatment

Table 2. Levodopa bioavailability, sc and LCIG

	Bioavailability sc AUC 0-infinity (%)	Bioavailability LCIG AUC 0-infinity (%)	Bioavailability sc AUC 0-16 h (%)	Bioavailability LCIG AUC 0-16 h (%)
Mean	104.4%	82.2%	94.7%	82.4%
SD	5.8%	8.7%	5.9%	8.9%
Min	98.0%	69.5%	89.4%	71.6%
Max	113.0%	89.6%	103.7%	91.2%
CoV	5.5%	10.6%	6.3%	10.8%

Table 3. Some pharmacokinetic variables of carbidopa in the first 5 patients

Variable	t1/2	Tmax	Cmax	AUC 0-infinity	Bioavailability
	h	h	ng/ml	ng/ml*h	%
Mean s.c.	2.85	14.40	1406	23548	102.4
Mean LCIG	3.93	7.10	290	4889	11.8
Mean i.v.	2.56	10.60	1038	17300	(100)
SD s.c.	0.39	2.61	506	8377	9.2
SD LCIG	0.75	5.46	77	1927	3.1
SD i.v.	0.35	3.58	370	5978	(0)

Local tolerability

All patients reported mild to moderate pain at initiation of s.c. infusion and 4/5 reported mild to moderate discomfort at initiation of iv infusion, both lasting throughout the high-speed bolus infusion period (<11 minutes). In three cases, some discomfort persisted at s.c. site for 1-8h. Three patients developed hematoma after >8h s.c. infusion. No severe adverse events were observed.

First four patients after protocol change (2M, 2F, age 55-74)

Table 4. Average and SD of levodopa doses in patient 6-9

Variable	Levodopa
Mean (SD) s.c.	1179 (332) mg
Mean (SD) LCIG	1343 (385) mg
Mean (SD) i.v.	1107 (313) mg

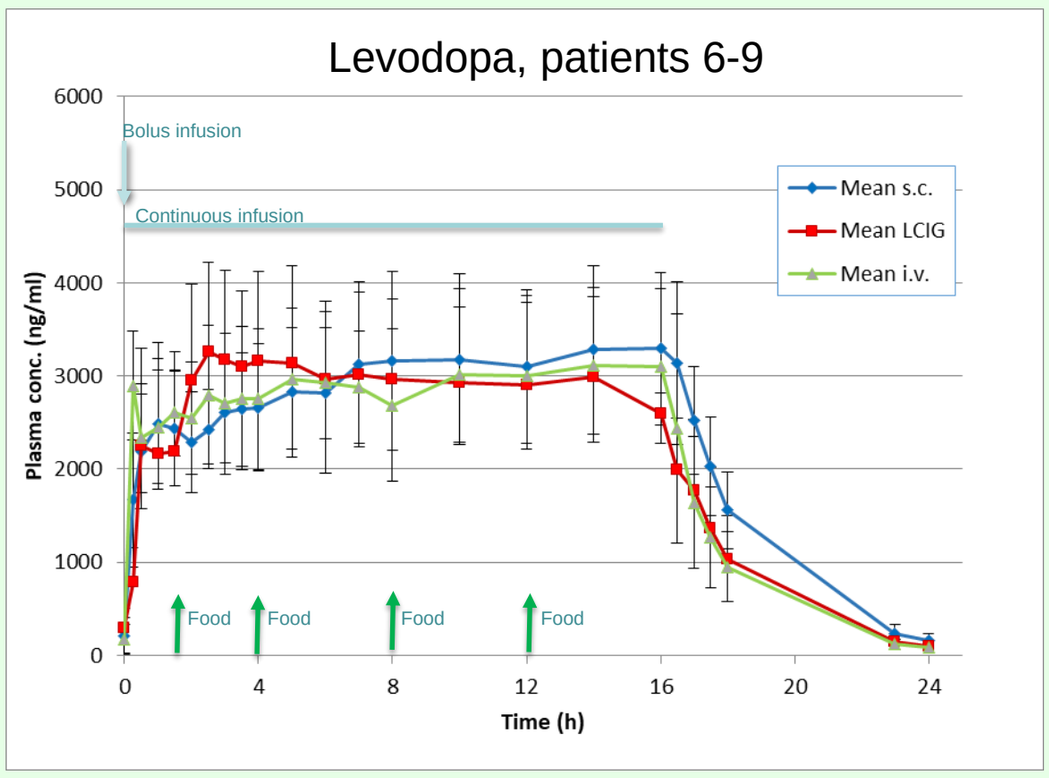

Figure 1. Plasma levels of levodopa during 16h infusion and up to 24h. Sc morning bolus was 155% of hourly levodopa dose, iv and LCIG bolus was 110%. Total administered iv levodopa dose was 82% and total sc dose was 88% of LCIG dose.

Local tolerability Infudopa SubC

The modified Infudopa SubC was not associated with hematoma development in the first four patients. Similar to original solution, all reported mild to moderate pain during bolus infusion and some mild tenderness or pinching intermittently during continuous infusion.

Summary

Online buffering is a feasible method for continuous subcutaneous or intravenous infusion of a concentrated levodopa/carbidopa solution to PD patients. Stable and sufficient levodopa concentrations can be reached rapidly following bolus infusions. Preliminary results indicate that the modified product Infudopa SubC reduces the risk of local hematoma following 16h infusions.

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