

# Novel administration routes for levodopa and dopamine agonists

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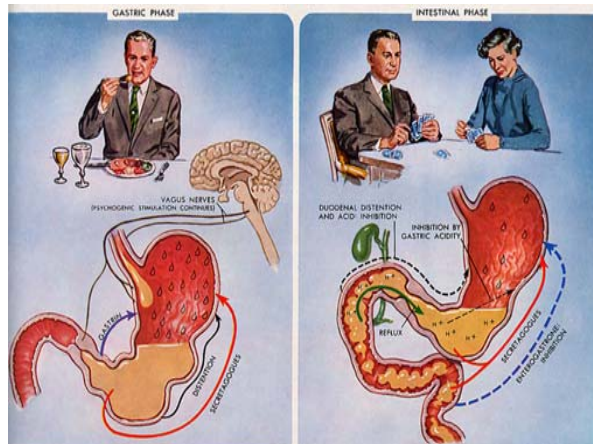
"It has become clear that the newer antiparkinsonian drugs have not solved the problem of response swings.

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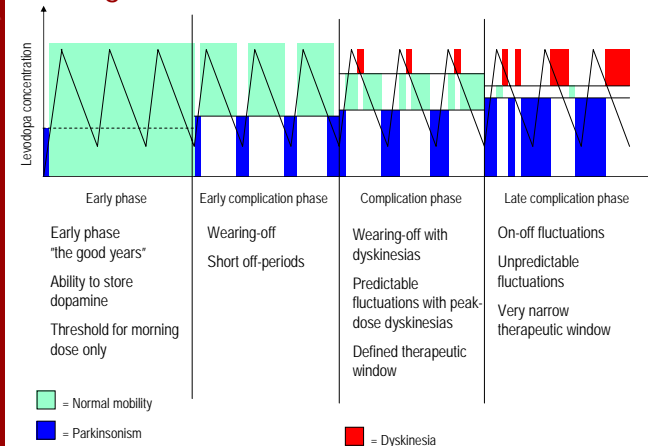
...new methods of delivery may have more to offer than new drugs"

Quinn et al. Neurology 1984

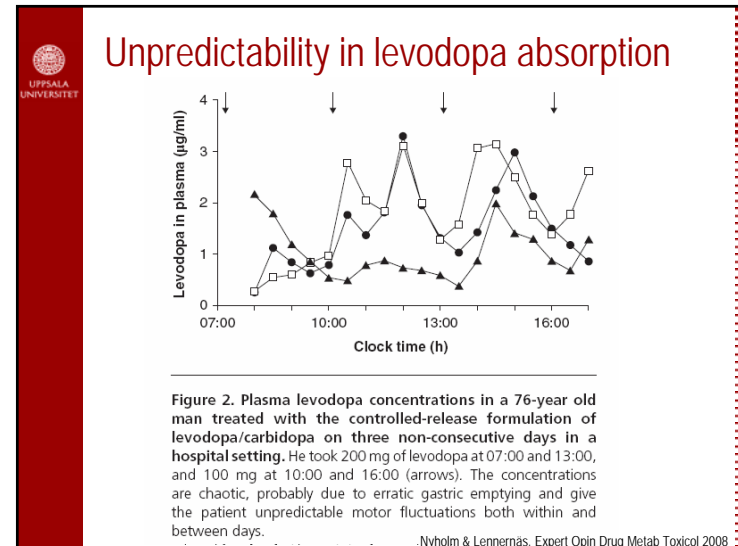
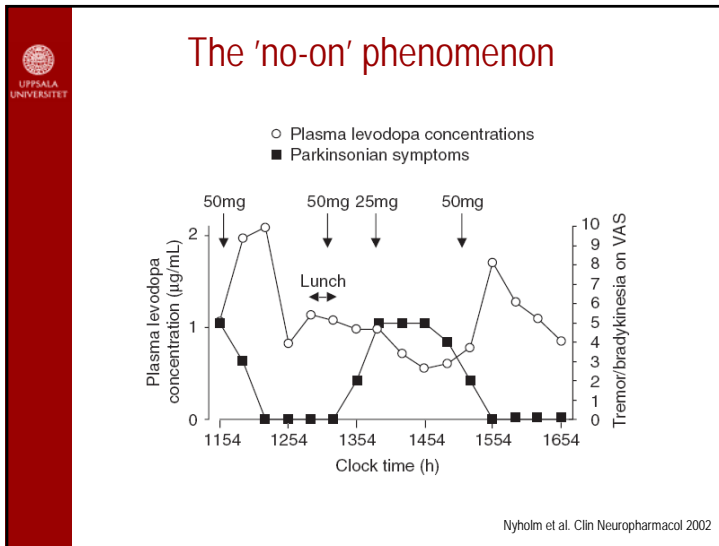
## Irregular gastric emptying



## Progression of Parkinson's disease



Nyholm. Parkinsonism Rel Disord 2007



**Routes of administration for levodopa**

Table II. Levodopa formulations and routes of administration alternative to standard levodopa tablets

Route of administration and formulation	Main differences in pharmacokinetics compared with standard levodopa	References
Enteral (duodenal/jejunal) infusion	↓ CV	60
Intravenous infusion	↓ CV	59
Nasal	NA	54
Oral dual release	↓ t <sub>max</sub> , ↑ C <sub>max</sub> , ↑ AUC compared with sustained-release formulation	61
Oral liquid	↓ t <sub>max</sub>	62,63
Oral sustained release	↑ t <sub>max</sub> , ↓ C <sub>max</sub> , ↓ CV	64
Pulmonary inhalation	NA	65

AUC = area under the plasma concentration-time curve; C<sub>max</sub> = peak plasma concentration; CV = coefficient of variation of plasma concentration (standard deviation divided by the mean plasma concentration); NA = not available; t<sub>max</sub> = time to reach C<sub>max</sub>; ↓ indicates decreased; ↑ indicates increased.

Nyholm. Clin Pharmacokinet 2006; 45 (2): 109-136

**Methods to circumvent gastric emptying**

Rescue medication  
Injections, inhalations

Continuous administration  
Infusions, patches, implants

## Non-oral routes of administration

Table III. Non-oral routes of administration of pharmacotherapy in Parkinson's disease

Route of administration	Drugs
Enteral (duodenal/jejunal)	Levodopa, levodopa esters
Intramuscular	Levodopa esters
Intravenous	Apomorphine, levodopa, levodopa esters, lisuride
Nasal	Apomorphine, levodopa <sup>a</sup>
Pulmonary	Levodopa <sup>a</sup>
Rectal	Apomorphine
Subcutaneous	Apomorphine, levodopa esters, lisuride
Sublingual/buccal	Apomorphine, levodopa esters, selegiline (deprenyl)
Transdermal	Apomorphine, bromocriptine, <sup>a</sup> levodopa esters, <sup>a</sup> lisuride, piribedil, rotigotine, selegiline

<sup>a</sup> Not tested in humans.

Nyholm. Clin Pharmacokinet 2006; 45 (2): 109-136

## Available non-oral drugs at present

- Transdermal rotigotine
- Subcutaneous apomorphine
- Duodenal levodopa

## Rotigotine patch (Neupro<sup>®</sup>)

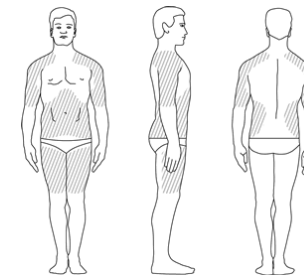


D<sub>3</sub>/D<sub>2</sub>/D<sub>1</sub> receptor affinity  
24-hour application



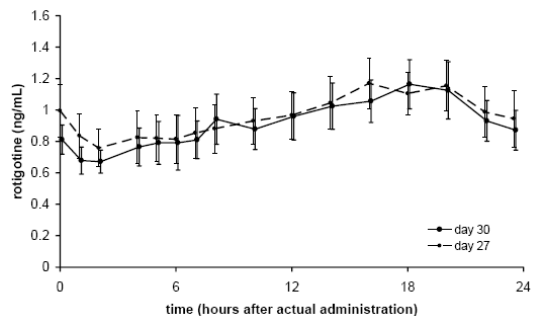
Drug-delivery proportional to patch size  
2 mg (10 cm<sup>2</sup>), 4 mg (20 cm<sup>2</sup>), 6 mg (30 cm<sup>2</sup>), 8 mg (40 cm<sup>2</sup>)

## Patch application sites



Difference in bioavailability shoulder-thigh 64%,  
"considered acceptable"  
(Baldwin & Keating. CNS Drugs 2007)

## Pharmacokinetics of rotigotine



## Efficacy of rotigotine

- Significant OFF reduction compared to placebo
- Significant increase in ON time without troublesome dyskinesia
- Similar to oral dopamine agonists (ropinirole and pramipexole)

LeWitt et al. Neurology 2007; Poewe et al., Lancet Neurol 2007

## Side-effects of rotigotine

Typical dopaminergic side-effects (nausea, dizziness, dyskinesias, hypotension)

Application site reactions (erythema, pruritus, dermatitis) in about half of the patients

Withdrawal from rotigotine due to skin reactions in 1-8%

## Apomorphine injections (Apo-go®)

- Potent D<sub>1</sub>/D<sub>2</sub> agonist
- Injections as needed, subcutaneously, 1-10 mg
- Time to onset 5-10 minutes
- Duration of effect 30-150 minutes
- "Rescue" from wearing-off
- Co-treatment with peripheral dopamine antagonist domperidone to avoid nausea/vomiting



Deleu et al., Drugs Aging 2004

## Efficacy of apomorphine injections

Decreased OFF time ~ 50%  
At the risk of increased dyskinesias ~ 33%

Deleu et al., Drugs Aging 2004

## Side-effects of apomorphine

Typical dopaminergic side-effects (nausea, dizziness, dyskinesias, hypotension)

Skin reactions, mainly fibrotic nodules (11% in patients with injections and 70% in patients with infusion)

Deleu et al., Drugs Aging 2004

## Apomorphine infusion



Continuous subcutaneous infusion  
Usually 1-5 mg/hour  
Sometimes monotherapy (Manson et al., 2002)

## Efficacy of apomorphine infusion

Decreased OFF time ~ 60%  
Decreased dyskinesias ~ 50%  
Decreased oral levodopa requirement ~ 50%

Deleu et al., Drugs Aging 2004

## Apomorphine infusion vs STN-DBS

7 + 9 patients, not randomised

Comparable improvement

**STN-DBS group:**  
moderate worsening in phonetic verbal fluency and Stroop Naming scores, partially reversible at long-term follow-up

Alegret et al. *Mov Disord* 2004;19:1463-1469

## Apomorphine infusion vs STN-DBS

12 months follow-up of 13 + 12 patients, not randomised

	Apomorphine infusion (daytime)	STN-DBS
Off time	-51%	-76%
AIMS	+3%	-81%
NPI	+0.8	+11.6 (apathy, anxiety, depression)

De Gaspari et al. *JNNP* 2006;77:450-453

## Neuropsychiatric adverse events

### STN-DBS

Cognitive disturbances  
Decline in word fluency, verbal memory, executivity  
Emotional lability, decreased positive affect  
Depression  
Suicide

(Hamani et al. *Neurosurg* 2005;56:1313-1324; De Gaspari et al. *JNNP* 2006;77:450-453; Deuschl et al. *NEJM* 2006;355:896-908; Smeding et al. *Neurology* 2006;66:1830-1836; Voon et al., *Mov Disord* 2006;21(Suppl 14):S305-S326)

### Apomorphine and levodopa infusions

#### Confusion, hallucinations

(Deleu et al. *Drugs Aging* 2004;21:687-709; Nyholm & Aquilonius *Clin Neuropharmacol* 2004;27:245-256)

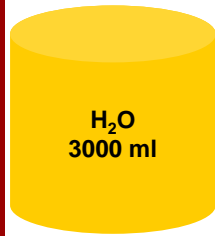


Based on 36 original articles

## Galenic formulation issue

Poor solubility of levodopa:

- large infusion volume of levodopa solution
- not possible in practice



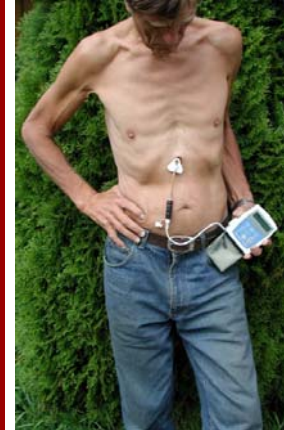
Levodopa 2,000 mg  
Carbidopa 500 mg



**Duodopa®**  
a highly concentrated  
intestinal gel formulation of  
Levodopa / Carbidopa



## Levodopa/carbidopa (Duodopa®)



L-dopa/carbidopa (20/5 mg/ml)  
in gel suspension,  
physical and chemical stability

PEG with duodenal tube

Ambulatory pump  
- continuous daytime infusion

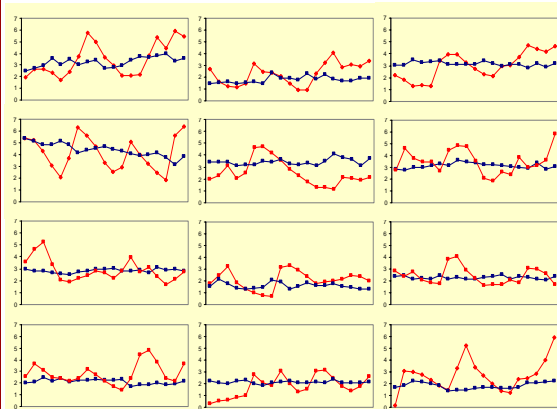
Mostly monotherapy



Sten-Magnus  
Aquilonius

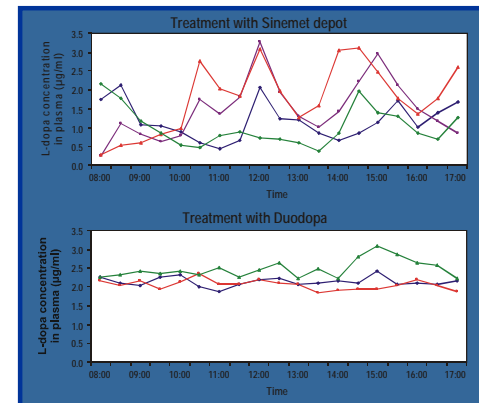
## Pharmacokinetics of Sinemet® CR / Duodopa®

L-dopa in plasma ( $\mu\text{g/ml}$ ) during 9 hours in 12 patients



Nyholm et al.,  
2003

## Plasma levodopa concentrations in one patient



Nyholm et al.,  
2003

## DIREQT

### Duodopa Infusion - Randomised Efficacy and Quality of life Trial

- Duodopa monotherapy vs any combination of conventional medication
- 24 patients, 5 centres in Sweden
- Video recordings, "blinded" scoring
- Efficacy and QoL - electronic home diary

Nyholm et al., 2005

## DIREQT – results

### Duodopa Infusion - Randomised Efficacy and Quality of life Trial

With Duodopa:

- Significantly increased number of observations in functional ON state
- Significantly decreased number of observations in OFF state
- Significantly improved UPDRS scores
- Significantly improved quality of life (PDQ-39 and 15D)

## Efficacy of levodopa/carbidopa infusion

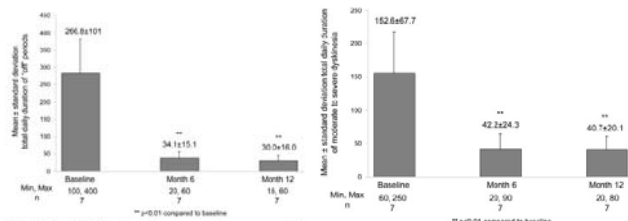


FIG. 2. Total daily duration (minutes) of moderate to severe "off" periods: observation period from 8:00 AM to 10:00 PM.

FIG. 3. Total daily duration (minutes) of moderate to severe dyskinesia: observation period from 8:00 AM to 10:00 PM.

Antonini et al. Mov Disord 2007

## Side-effects of levodopa/carbidopa infusion

Typical dopaminergic side-effects (nausea, dizziness, dyskinesias, hypotension)

Tube dislocations

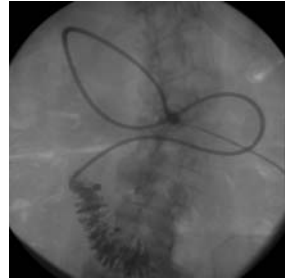
Skin reactions (hypergranulation tissue)

Nyholm et al. Clin Neuropharmacol 2008

## Duodenal/jejunal tube



Bengmark tube  
Used for Duodopa since Sep 2001

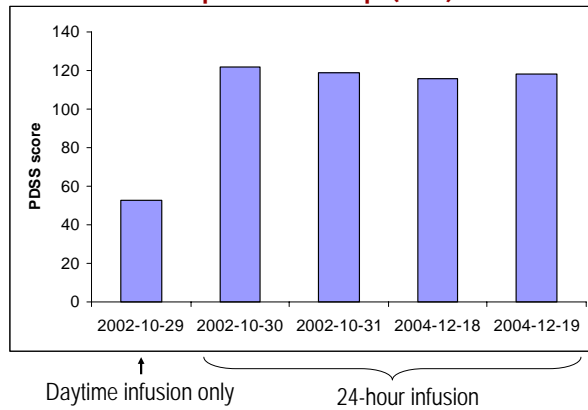


Good jejunal position on X-ray

## Non-motor symptoms

- Important, may be misinterpreted
- Pain
- Depression
- Anxiety
- Cognitive impairment
- Sleep disturbance
- Etc...

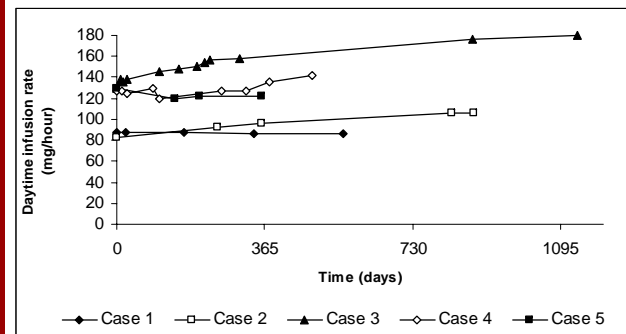
## 24-hour levodopa infusion – impact on sleep (n=1)



PD Sleep Scale. Maximum: 150, HY stage 4-5: ~90 (Chaudhuri et al., 2002)

Nyholm et al., 2005b

## 24-hour levodopa infusion and dose requirements



Nyholm et al., 2005b

## Neuroprotection?

- CDS theory
- Animal models
- Imaging
- Progress of PD
- Dose requirement



## Stable dosage over time

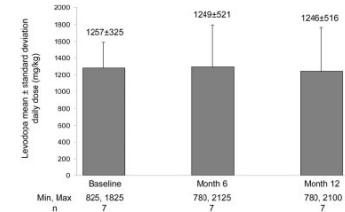


FIG. 1. Daily administered dose of levodopa. Baseline dose refers to total levodopa equivalents (levodopa + dopamine agonists), whereas 6- and 12-month dose refer to total infused levodopa.

Antonini et al. Mov Disord 2007

Average levodopa dose decreased by 5% in 58 patients during 3.7 years of levodopa infusion

Nyholm et al. Clin Neuropharmacol 2008

## Special situations where non-oral therapy may be useful

- Non-motor fluctuations
- Nighttime disability
- Dysphagia
- Postoperatively
- Palliative care

## The perspective of the patient



Thank you!



Uppsala, Sweden