School of Pharmacy

Faculty of Medicine

The Chinese University of Hong Kong

Workshop in Celebration of 25th Anniversary of the School of Pharmacy

Biopharmaceutics of Modified Release Products and Challenging Drug Molecules

Combination products: A simulation study of BABE

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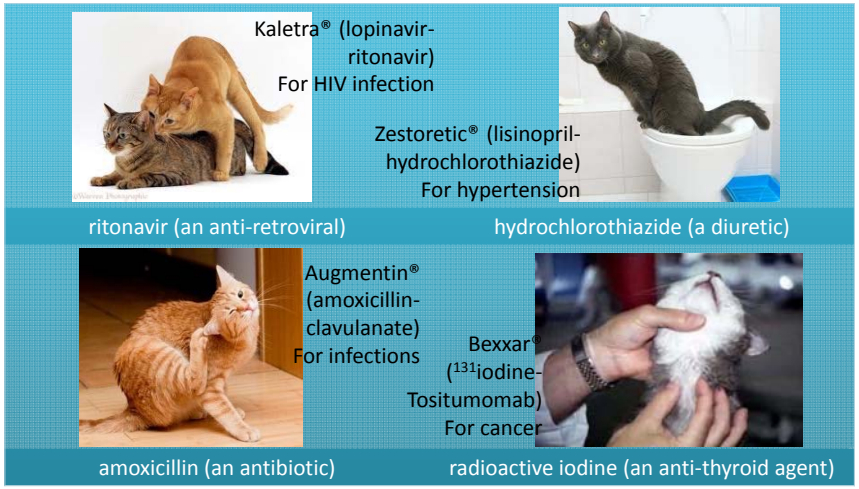
Presentation outline

- Fixed-dose combination products: rationale and challenges
- Carbidopa – levodopa combination
- Pharmacokinetic-pharmacodynamic modeling and simulation
- Simulation scenarios

Which of the following does NOT form a part of a marketed combination product?



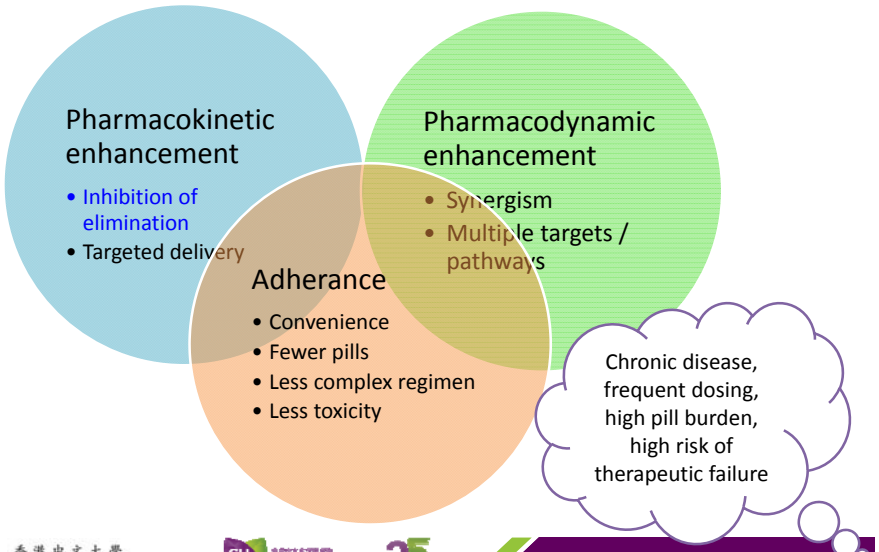
Fixed-dose combination products examples

- Anti-retrovirals
  - Protease inhibitor + booster (lopinavir + ritonavir)
  - "Cocktail" therapy (emtricitabine + tenofovir + efavirenz)
- Anti-infectives
  - Beta-lactam + beta-lactamase inhibitor (amoxicillin + clavulanate, ampicillin + sulbactam, piperacillin + tazobactam)
  - Folate biosynthesis inhibitors (trimethoprim + sulfamethoxazole)
- Parkinson disease
  - Dopamine precursor + metabolism inhibitor(s) (levodopa + carbidopa ± entacapone
- Analgesic
  - Opioid + non-opioid (codeine + paracetamol, tramadol + paracetamol)
- Cold / flu preparations
  - All-in-one combos (paracetamol + chlorpheniramine + dextromethorphan + caffeine + phenylephrine…)

Combination products : challenges

- What if… “an incorrect vial of ampicillin 2g was dispensed instead of ampicillin-sulbactam 1.5g?”

Rational Combination products : benefits

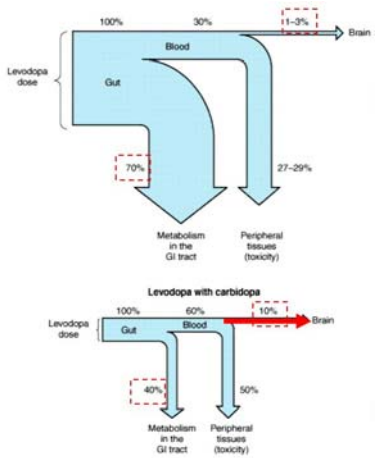


Levodopa : Pharmacokinetic enhancement by inhibition of elimination

Active ingredients	Strength	Name (Mfg.)
Levodopa	NONE (!)	NONE (!)
Carbidopa-Levodopa	25/100, 25/250	Sinemet (MSD) , Levomed, Levomet, (Apotex, Teva,)
Carbidopa-Levodopa (controlled release)	CR: 50/200	Sinemet CR (MSD)
Benserazide-Levodopa	25/100, 50/200	Madopar (Roche)
Benserazide-Levodopa (controlled release)	SR: 25/100	Madopar HBS SR (Roche)
Levodopa-Carbidopa-Entacapone	50/12.5/200, 75/18.5/200 100/25/200,125/31.25/200, 150/37.5/200, 200/50/200,	Stalevo (Novartis)

Entacapone is available by itself (Comtan 200mg), carbidopa and berserazide are not available by itself.

Carbidopa is a pharmacokinetic enhancer



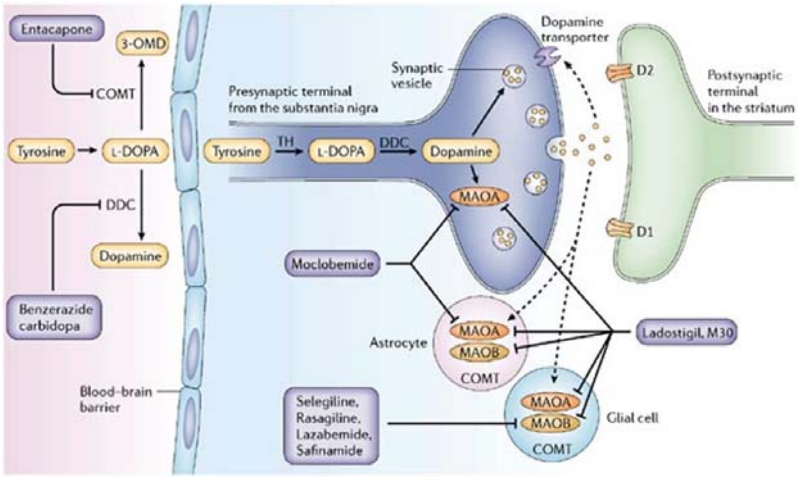
Levodopa
BCS class I. When give alone, its oral bioavailability is about 40% due to first pass metabolism

Carbidopa
BCS class I. When give alone, its oral bioavailability is about 60%.

Levodopa
When co-administered with carbidopa, its oral bioavailability increases to about 85%

Br. J. clin. Pharmac. (1989), 28, 61-69

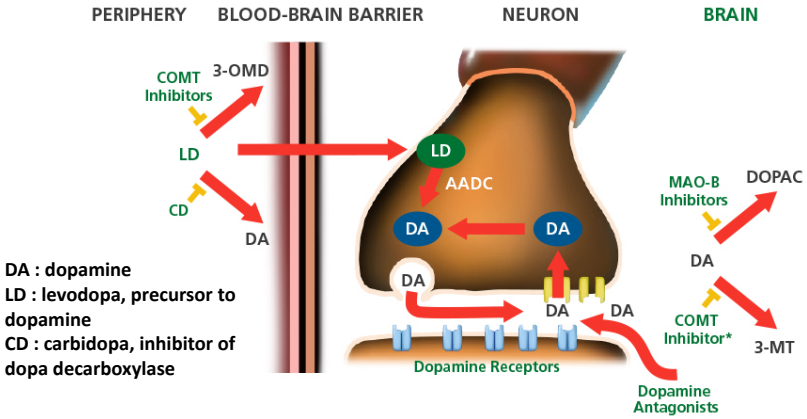
Pharmacotherapy of Parkinson's disease



Youdim *et al. Nature Reviews Neuroscience* **7**, 295–309 (April 2006) | doi:10.1038/nrn1883

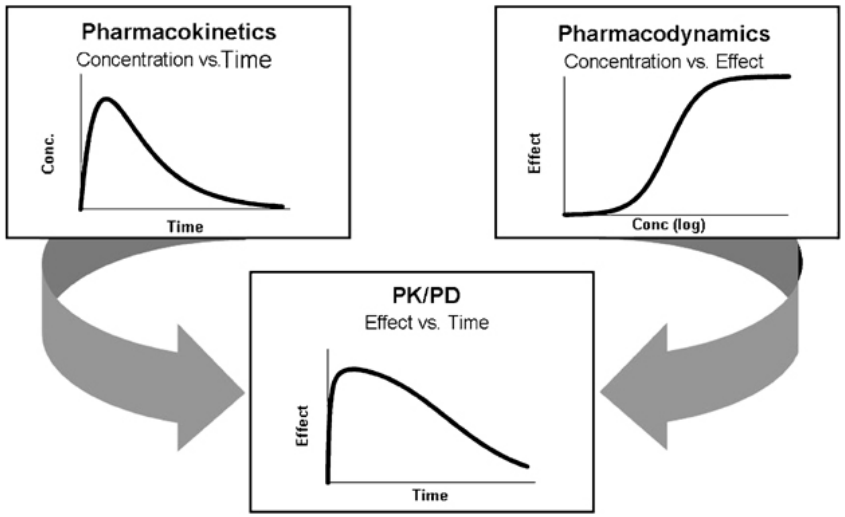
Pharmacology of carbidopa-levodopa

Parkinson's disease is characterized by a relative lack of dopaminergic transmission at motor neurons. The usual treatment strategy is to supplement dopamine activity.

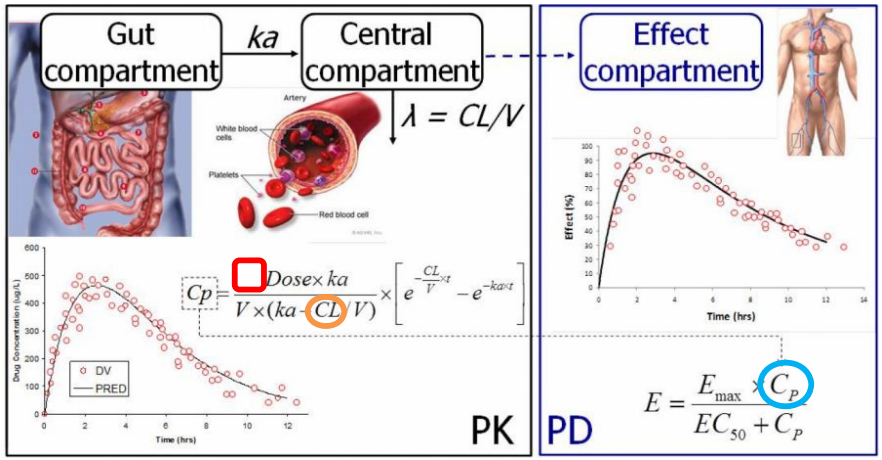


DA : dopamine
LD : levodopa, precursor to dopamine
CD : carbidopa, inhibitor of dopa decarboxylase

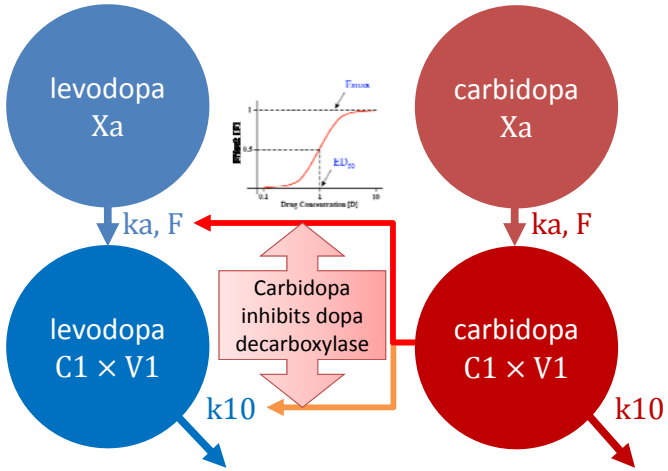
Dose-exposure-response relationship



Pharmacokinetic – pharmacodynamic model

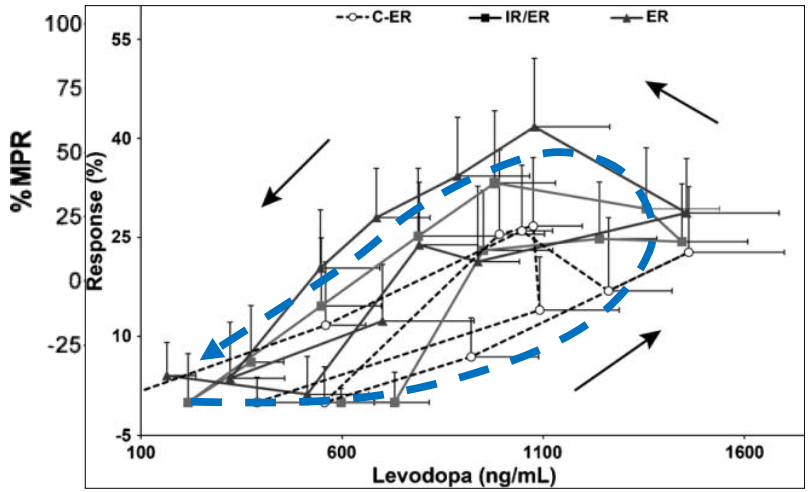


Dose-exposure relationship



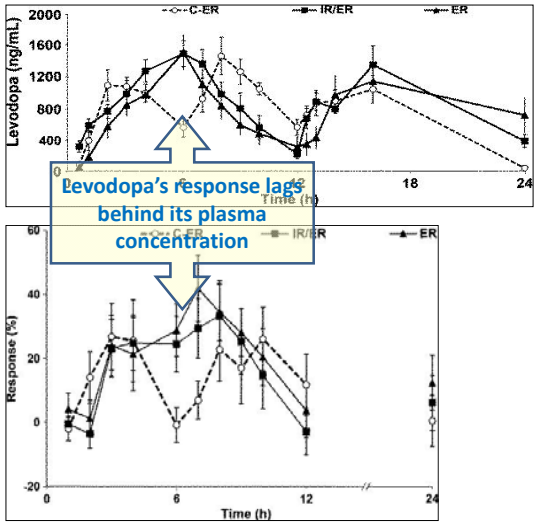
It has been demonstrated that pharmacokinetics of levodopa and carbidopa are well-described by linear one-compartment model.

Exposure-response relationship



Clinical Neuropharmacology. 35(2):67-72, March/April 2012.

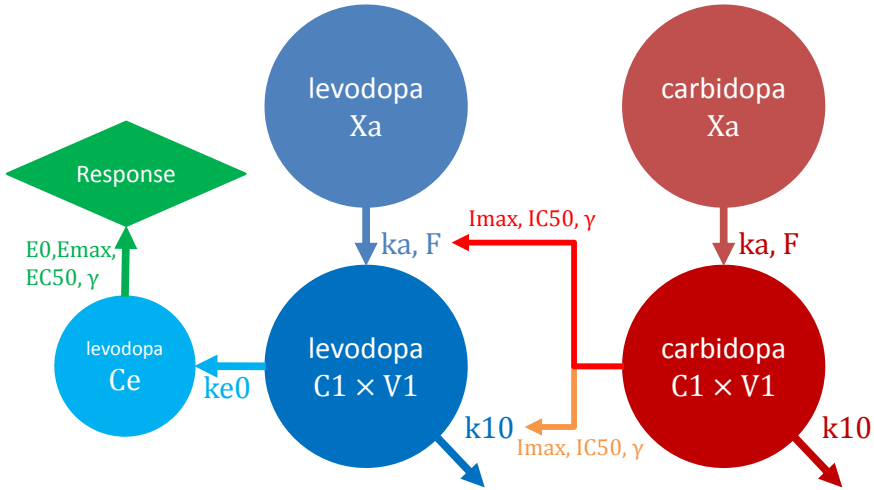
Exposure-response relationship



There's an "effect compartment" in describing levodopa's exposure-response relationship

Clinical Neuropharmacology. 35(2):67-72, March/April 2012.

Dose-exposure-response relationship



The simple PK/PD model contains 5 compartments and 21 parameters

PK/PD Model equations

$$\frac{dX_{LD}}{dt} = -k_{a,LD} \times X_{LD} \quad (1)$$ 1. Absorption of LD

$$\frac{dX_{CD}}{dt} = -k_{a,CD} \times X_{CD} \quad (2)$$ 2. Absorption of CD

$$\frac{dC1_{LD}}{dt} = \frac{k_{a,LD} \times F_{LD} \times X_{LD}}{V1_{LD}} - k_{10,LD} \times C1_{LD} \quad (3)$$ 3. Central cmpt of LD

$$\frac{dC1_{CD}}{dt} = \frac{k_{a,CD} \times F_{CD} \times X_{CD}}{V1_{CD}} - k_{10,CD} \times C1_{CD} \quad (4)$$ 4. Central cmpt of CD

$$\frac{dCe_{LD}}{dt} = k_{e0,LD} \times (C1_{LD} - Ce_{LD}) \quad (5)$$ 5. Effect cmpt of LD

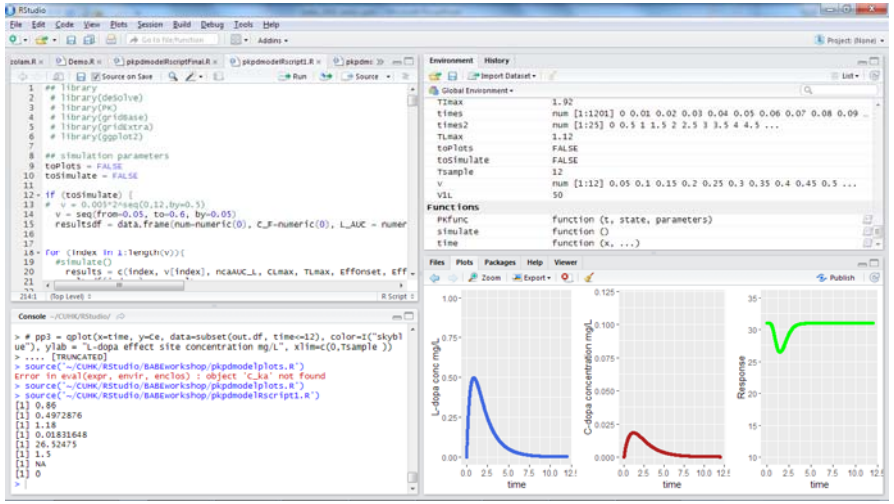
$$F_{LD} = F_0 + \frac{Imax_F \times {C1_{CD}}^{\gamma_F}}{{IC50_F}^{\gamma_F} + {C1_{CD}}^{\gamma_F}} \quad (6)$$ 6. Imax model on F_{LD}

$$k_{10,LD} = k_0 - \frac{Imax_k \times {C1_{CD}}^{\gamma_k}}{{IC50_k}^{\gamma_k} + {C1_{CD}}^{\gamma_k}} \quad (7)$$ 7. Imax model on k_{LD}

$$E = E_0 + \frac{Emax \times {Ce_{LD}}^{\gamma_E}}{{EC50_E}^{\gamma_E} + {Ce_{CD}}^{\gamma_E}} \quad (8)$$ 8. Emax model of E

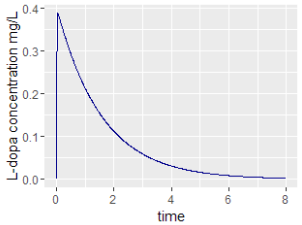
These ODEs can be solved efficiently with “deSolve” package in R

Demonstration



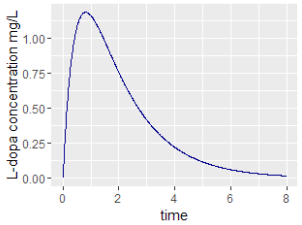
Qualifying our PK/PD model – Levodopa alone

IV dose 50mg



IV dose 50mg	Simulated	Reference
AUC	0.534	0.541 ± 0.140
CL	93.7	98.3 ± 17.2
Vss	171	132 ± 62.2
t½	1.27	1.3 ± 0.3

PO dose 250mg

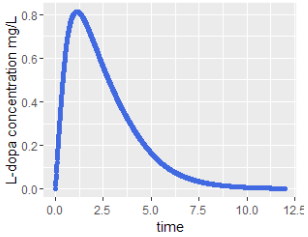


PO dose 250mg	Simulated	Reference
Cmax	1.19	1.08 ± 0.577
Tmax	0.81	0.8 ± 0.6
t½	1.45	1.5 ± 0.4

Br. J. clin. Pharmac. (1989), 28, 61-69

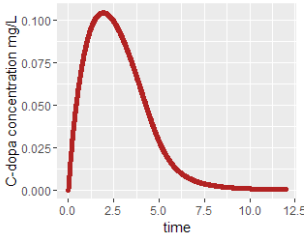
Qualifying our PK/PD model – Levodopa and carbidopa IR formulation

L-dopa 100mg IR



L-dopa 100mg	Simulated	Reference
AUC	2.675	2.251 ± 0.664
Cmax	0.812	1.094 ± 0.401
Tmax	1.12	1.0 ± 0.5
t½	1.76	1.6 ± 0.2

C-dopa 25mg IR

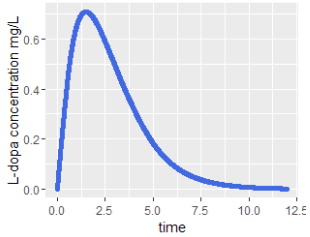


C-dopa 25mg	Simulated	Reference
AUC	0.398	0.448± 0.157
Cmax	0.104	0.106 ± 0.043
Tmax	1.92	2.5 ± 1.0
t½	1.91	1.8 ± 0.2

The Journal of Clinical Pharmacology 2015, 55(9) 995–1003

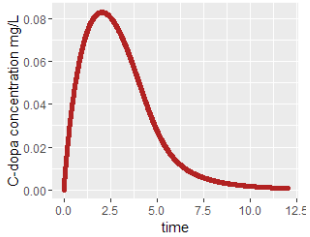
Qualifying our PK/PD model – Levodopa and carbidopa CR formulation

L-dopa 100mg CR



L-dopa 100mg	Simulated	Reference
AUC	2.582	2.403 ± 0.680
Cmax	0.707	0.855 ± 0.299
Tmax	1.49	1.5 ± 0.5
t½	1.92	1.6 ± 0.2

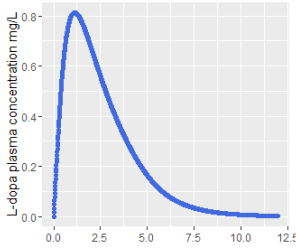
C-dopa 25mg CR

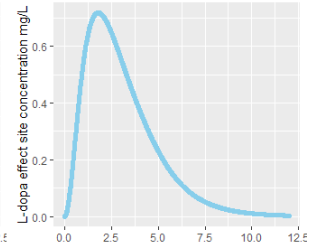


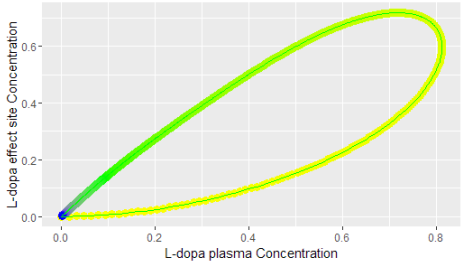
C-dopa 25mg	Simulated	Reference
AUC	0.340	0.373± 0.117
Cmax	0.083	0.086 ± 0.032
Tmax	2.04	3.0 ± 1.0
t½	2.11	2.0 ± 0.4

The Journal of Clinical Pharmacology 2015, 55(9) 995–1003

Qualifying our PK/PD model – (25/100 IR) Cp and Ce relationships



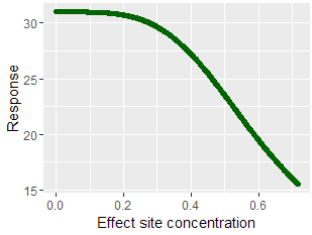


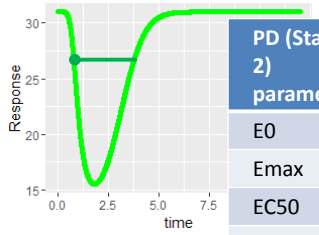


PK-PD link parameters	Reference value
ke0	1.86

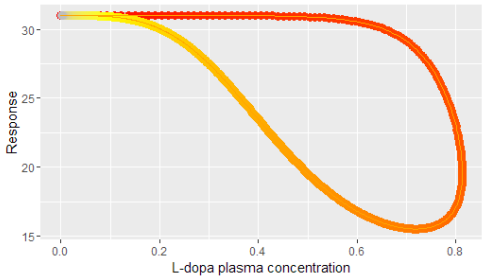
Clin Neuropharm 2010;33: 135Y141

Qualifying our PK/PD model – (25/100 IR) Cp, Ce and Response relationships

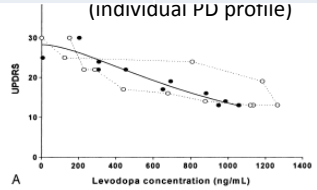




PD (Stage 2) parameters	Reference value
E0	31
Emax	23
EC50	0.6
slope	4

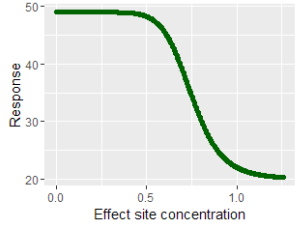


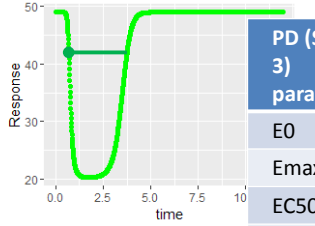
(individual PD profile)



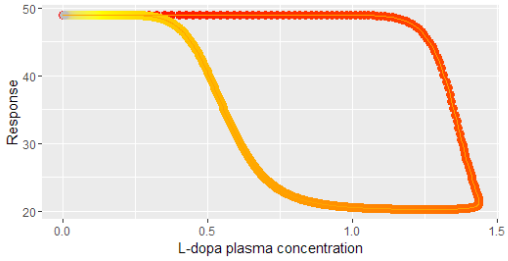
Clin Neuropharm 2010;33: 135Y141

Qualifying our PK/PD model – (20/200 IR) Cp, Ce and Response relationships

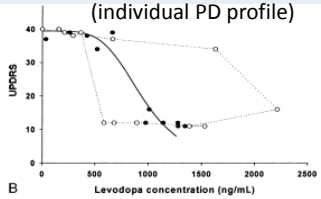




PD (Stage 3) parameters	Reference value
E0	49
Emax	29
EC50	0.75
slope	9



(individual PD profile)

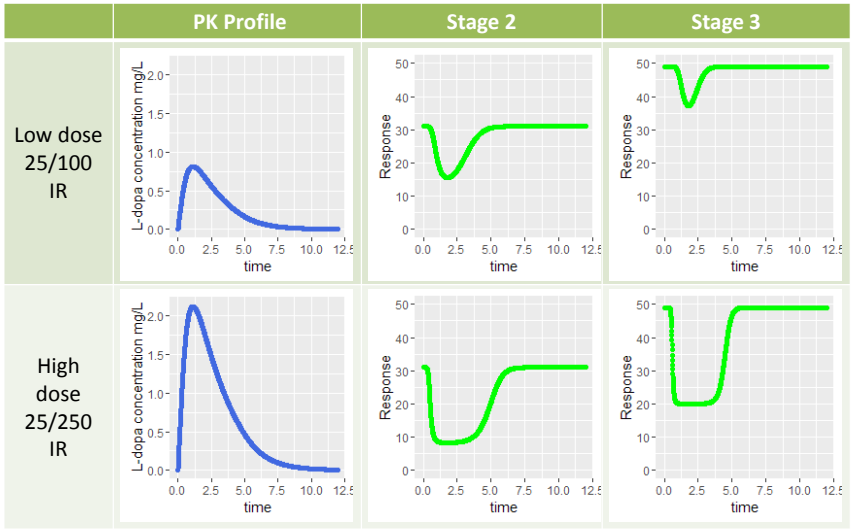


Clin Neuropharm 2010;33: 135Y141

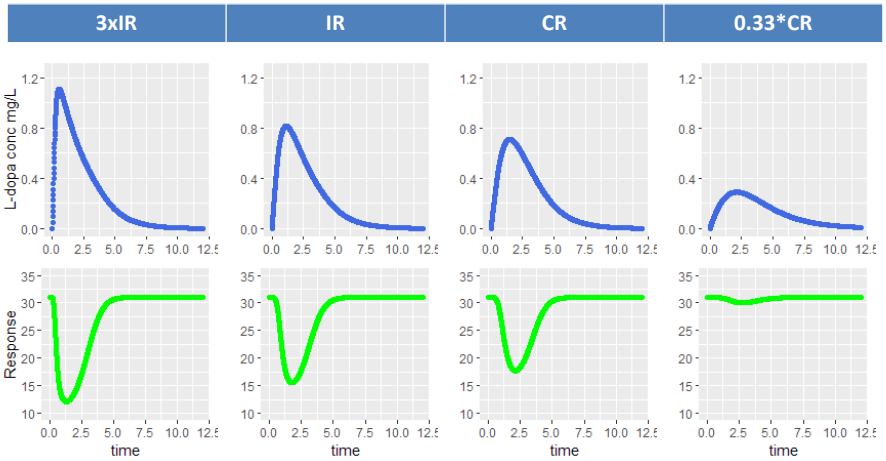
Assumptions and limitations

- Simplistic pharmacokinetic and pharmacodynamic models
  - Did not attempt to evaluate model specification and/or parameterization
- No model for drug release, disease progression or covariate
  - Old age, advanced disease appeared to have altered disposition
- Individual and deterministic simulations
  - Only point estimates and no variability and uncertainty
- Limited qualification of model predictions
  - Only compared to PK parameter values in literature
  - Based on multiple literature reports, which were not totally consistent

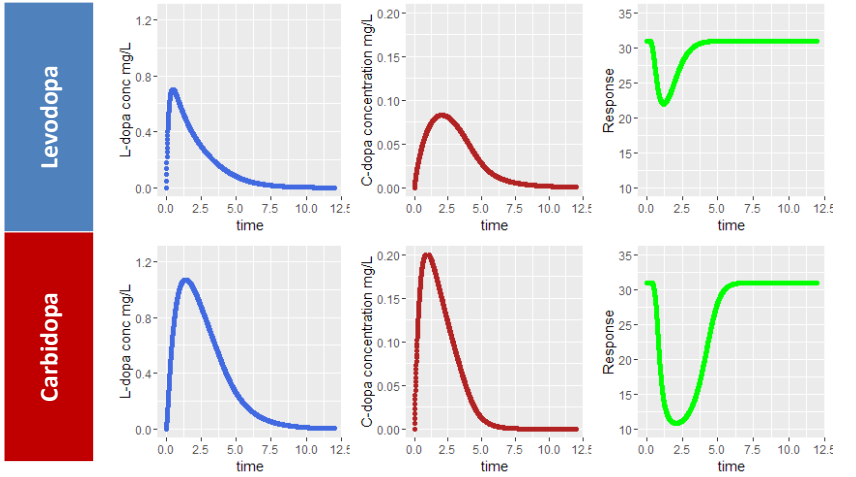
Simulation scenario – advanced disease



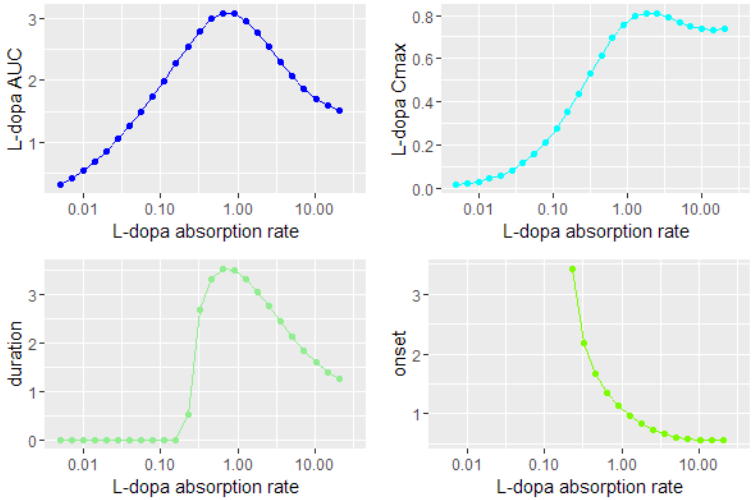
Simulation scenario – dose dumping / prolonged release



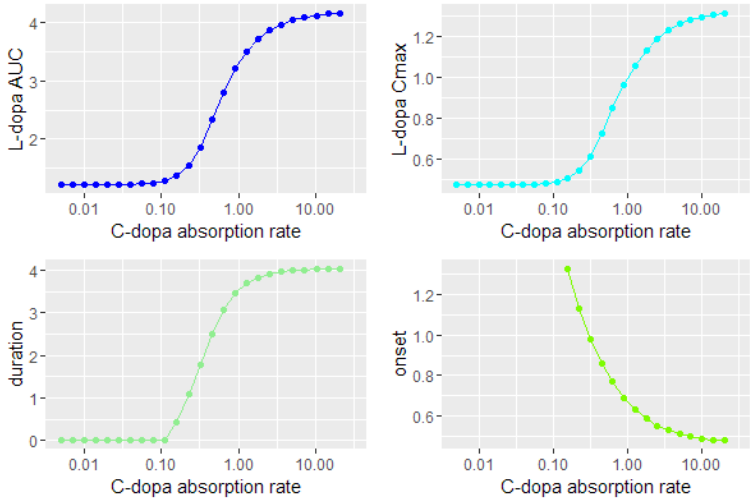
Simulation scenario – dose dumping of 1 active ingredient only



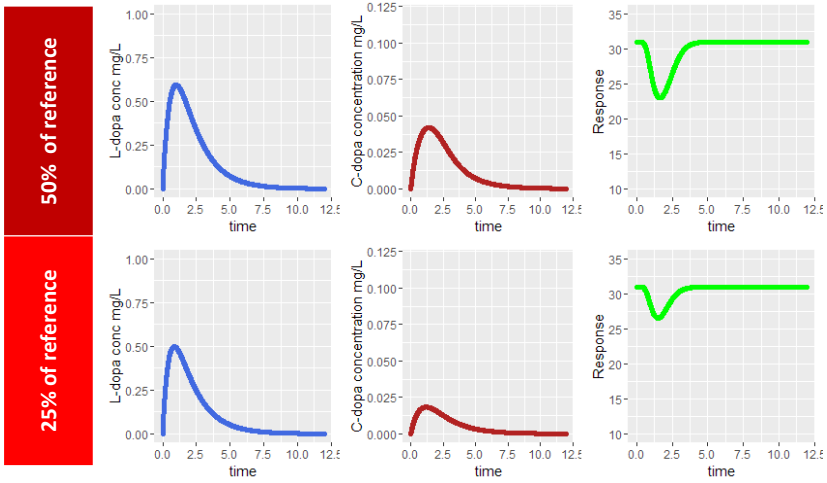
Simulation: effect of absorption rate (L)



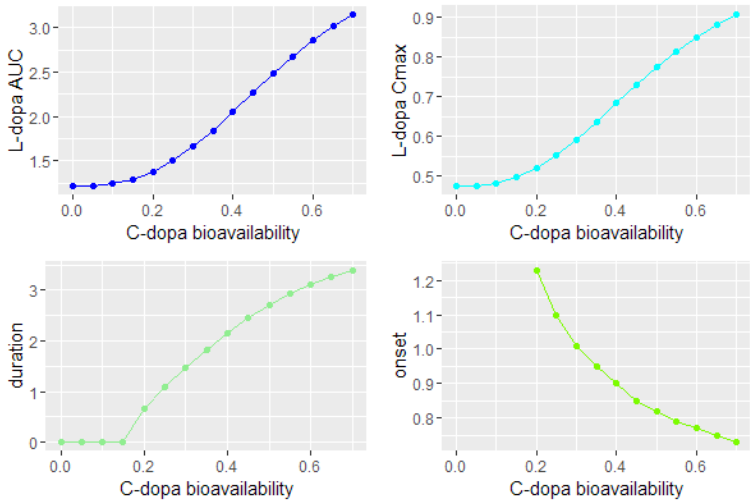
Simulation: effect of absorption rate (C)



Simulation scenario – food reduces bioavailability of carbidopa



Simulation: effect of bioavailability (C)



Thoughts on bioavailability

- Carbidopa seems to provide a window of protection
  - Exposure of levodopa can be enhanced as long as levodopa is released /absorbed when carbidopa is present at a sufficient concentration
  - Simulation shows that the optimal absorption profile is when both drug are absorbed at similar rate, or when the inhibitor is slightly faster
  - Both absorption rate and extent of the inhibitor are critical factors of levodopa absorption, yet the acceptable window appears to be wide.