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Population Pharmacokinetic of L-DOPA and its main metabolites: Use of the Phoenix based ORPEM algorithm

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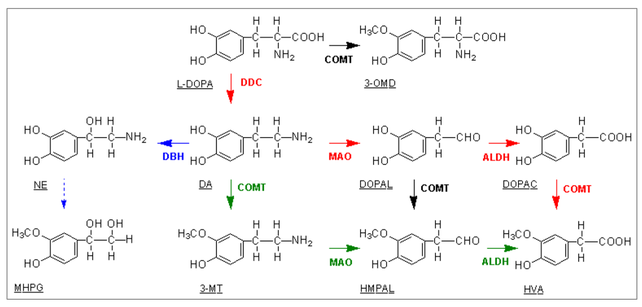
BACKGROUND

- Selective deuteration at the alpha and beta carbon in the side chain of L-DOPA has been shown to attenuate the metabolism of the deuterated dopamine derived from this molecule (Malmlöf 2008).
- Nonclinical studies confirmed that the kinetic isotope effect attenuates the metabolism of deuterated dopamine by monomine oxidase (MAO), the main metabolic pathway, and by dopamine beta-hydroxylase (DBH) to norepinephrine.
- Reduced rates of metabolism but also metabolic switching, a change from one metabolic site to a different site, has been shown as result of selective deuteration in different molecules (Harbeson 2014). Those effects need to be evaluated during the development of a deuterated drug candidate.
- Different sites of L-DOPA metabolism, an extremely short half life of dopamine in plasma and reabsorption of L-DOPA and its metabolite 3-O-methyldopa (3-OMD) make it difficult to establish a predictive PK model for L-DOPA that also can account for deuterium kinetic isotope effects.
- L-DOPA and its metabolites are mainly excreted via urine. Therefore the model includes both plasma concentrations of L-DOPA and its main metabolites and amounts excreted into urine.

Figure 1. L-DOPA Metabolism



Abbreviations. Compounds: 3-OMD = 3-O-methyldopa, NE = norepinephrine, DA = dopamine, DOPAL = 3,4-dihydroxyphenylacetaldehyde, DOPAC = 3,4-dihydroxyphenylacetic acid, MHPG = 3-Methoxy-4-hydroxyphenylglycol, 3-MT = 3-methyoxytyramine, HMPAL = 4-hydroxy-3-methoxyphenyl acetaldehyde, HVA= homovanillic acid. Enzymes: DDC = dopa decarboxylase, MAO = monoamine oxidase, COMT = catechol O-methyltransferase, DBH = dopamine b-hydroxylase, ALDH = aldehyde dehydrogenase

OBJECTIVES

- To obtain population PK characteristics of L-DOPA and its metabolites in plasma and urine using the parametric, non-linear mixed effect modelling with Phoenix NLME.
- To show the advantage of QRPEM algorithm compared to standard FOCE-ELS.
- To present a new parallelization technique using large grid computing resources to solve complex problems without time consuming runs.

METHODS

- Blood and urine concentration over 24 hours were determined after administration of 37.5 mg carbidopa (tablets) and 150 mg L-DOPA (oral solution) 30 min after carbidopa to 11 healthy subjects. Time profiles of L-DOPA, dopamine, DOPAC, HVA and 3-OMD in plasma and cumulative amounts in urine were modeled simultaneously including double peak, and extravascular formation of dopamine.
- Optimization was achieved with a new accurate parametric EM method QRPEM in Phoenix NLME that uses low discrepancy Sobol sequences, as opposed to the stochastic Monte Carlo sampling technique.
- Locally initiated model runs were sent to remote computing platforms for execution and results returned to the local application using parallelization techniques in Phoenix 8 and a 300 core SGE grid hosted on Amazon Web Services by means of CFN grid software.

RESULTS

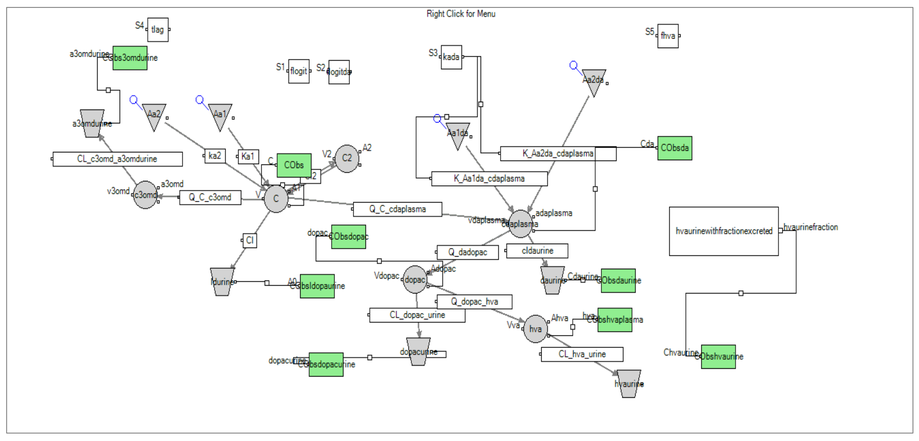
PROCESSES INVOLVED

- L-DOPA Drug dose input
  - 2 absorptions sites, separated by tlag
    - Fraction is absorbed immediately while the remaining fraction is absorbed after tlag
  - Extravascular immediate equilibrium between L-DOPA and DOPAMINE resulting in only a fraction of L-DOPA from the 2 sites entering Plasma In Plasma
- Plasma first order metabolic transfer L-DOPA->DOPAMINE->DOPAC->HVA
- Plasma first order metabolic transfer L-DOPA->3-OMD
- L-DOPA First order transfer central/peripheral to peripheral/central
- First order clearance of L-DOPA into urine
- First order clearance of DOPAMINE into urine
- First order clearance of DOPAC into urine
- First order clearance of HVA into urine
- First order clearance of 3-OMD into urine

Optimization Algorithm

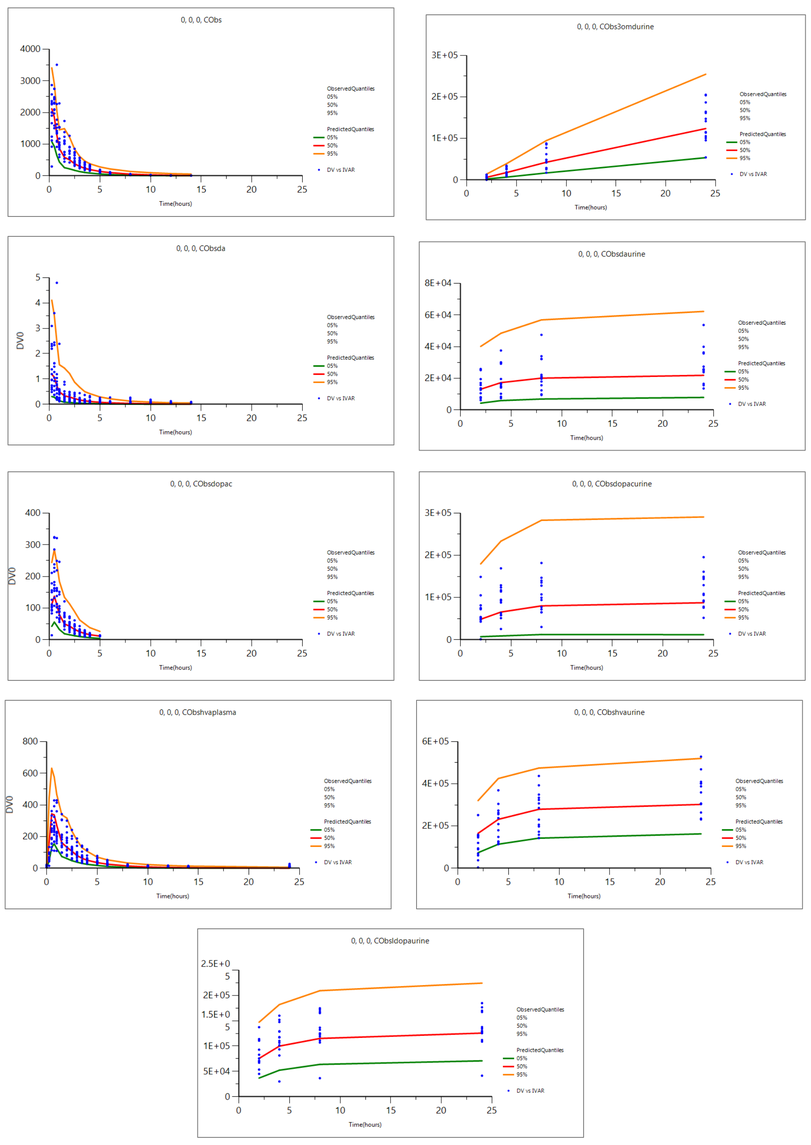
- The estimation of the parameters was extremely complex and involved
  - Regular optimization using maximum likelihood
  - Adjustment for some of the mean parameters
  - Bayesian individual estimations for estimating some of the variances that could not be estimated using regular optimization algorithms because of 13 patients with 24 fixed effect parameters(mean parameters)
- The model estimated 23 fixed and 23 random effects.
- Only QRPEM had enough driving force for optimal minimization.
  - FOCE-ELS locked multiple times into local minimums with bad diagnostics.
- Optimization was performed sequentially, starting with the fit of L-DOPA and dopamine data. The corresponding clearance terms split across the different paths. This resulted in satisfactory goodness-of-fit, good concordance between observed and simulated visual predictive checks and very good individual Bayesian fits for all responses.
- The new technique shortened run times significantly.
- Precision of parameters could not be assessed because the number of fixed effect parameter estimates was larger than individuals.

Figure 2. Parent/Metabolite Model



Parameter	Estimate	Unit	Definition
tvV	115.468	ml/kg	LDOPA volume of distribution
tvCl	35.0582	ml/kg/hr	Urine LDOPA clearance
tvKa1	2.13225	1/hr	Ldopa absorption from site 1 into plasma
tvka2	0.395453	1/hr	Ldopa absorption from site 2 into plasma
tvV2	243.99	ml/kg	LDOPA peripheral volume of distribution
tvCl2	125.493	ml/kg	LDOPA Inter compartmental clearance
tvflogit	0.617825	None	fractionLDOPA drug absorbed from first site
tvflogitda	2.40298	None	Bioavailability in the logit domain(~90% bioavailability)
tvvdaplasma	510.614	ml/kg	Dopamine volume of distribution
tvQ_C_cdaplasma	367.871	ml/kg/hr	Flow from LDOPA to dopamine
tvkada	0.0292433	1/hr	absorption dopamine into plasma
tvcldaurine	10010.9	ml/kg/hr	Dopamine clearance into urine
tvtlag	1.33242	Hours	delay in dosing relative to true dosing time
tvv3omd	437.717	ml/kg	OMD volume of distribution
tvQ_C_c3omd	88.7012	ml/kg/hr	Flow LDOPA into 3OMD
tvCL_c3omd_a3omdurine	11.6955	ml/kg/hr	Urine clearance 3OMD
tvVdopac	496.101	ml/kg	DOPAC volume of distribution
tvQ_dadopac	600747	ml/kg/hr	Flow dopamine into DOPAC
tvCL_dopac_urine	327.629	ml/kg/hr	DOPAC urine clearance
tvVva	200.271	ml/kg	HVA volume of distribution
tvQ_dopac_hva	4326.1	ml/kg/hr	Flow DOPAC into HVA
tvCL_hva_urine	1501.97	ml/kg/hr	HVA urine clearance
tvfhva	-1.0985	none	fraction urine excreted (in the logit domain),~25% fraction excreted

Visual Predictive Check



CONCLUSIONS

- A complex PK/Metabolite model has been developed and fit to the data using a combination of optimization, adjustment and Bayesian algorithm to finally reach very good fitting properties.
- The population predictions (VPC) were excellent.
- The average predictions were in the middle of the observed data with very small bias.
- This model can be used for extrapolation to any dosage regimen but requires Carbidopa to be in excess (e.g. 1 to 4 ratio of carbidopa to L-DOPA).

REFERENCES

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2. Harbeson SL and Tung RD. (2014). Deuterium Medicinal Chemistry: A new approach to drug discovery and development. *MedChem News*; 2:8-22.

DISCLOSURES

SG is a consultant for Teva Pharmaceutical Industries. NT is an employee of Certara. ML, SG, and FS are employees of Teva Pharmaceutical Industries.

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