

Analysing the Contribution to Receptor Occupancy from Active Metabolites

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Introduction

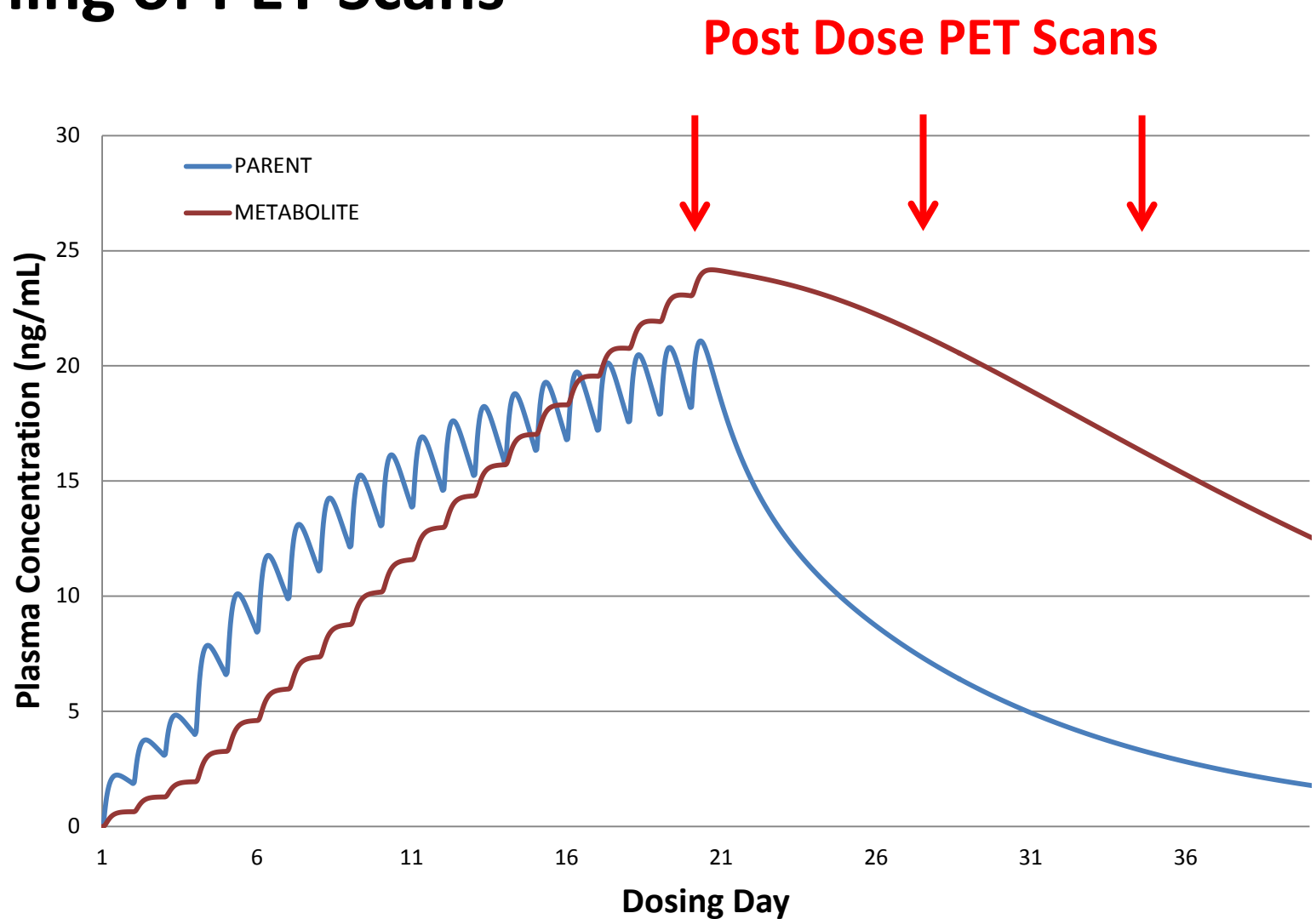
- A human positron emission tomography (PET) study was conducted to evaluate receptor occupancy of a drug after multiple dosing
- The drug and its major active metabolite have long elimination half-lives (150 and 250 hour, respectively)
- The study was designed to facilitate an evaluation of the contribution of the metabolite to the receptor occupancy

Objective

- To present a study design and modelling approach for investigating the contribution to receptor occupancy from active metabolites with longer terminal half-lives than the parent compound

PET Study Design

Timing of PET Scans



Study Design Simulated plasma concentrations of parent and metabolite. Days 1-3: 10 mg/Day and Days 4-20: 20 mg/day. PET scans performed at baseline Day 1 and 8H, Day 7 and Day 14 after last dose to obtain largest difference between parent and metabolite concentrations and thus to reduce collinearity.¹

Dosing

- 2 subjects received: Days 1-21: 10 mg/day
- 2 subjects received: Days 1-3: 10 mg/day; Days 4-21: 15 mg/day
- 2 subjects received: Days 1-3: 10 mg/day; Days 4-20: 20 mg/day

PET Methodology

- In all PET scans, one venous catheter for injection of radiotracer was placed at least 20 minutes prior to administration of the PET-tracer
- The primary region of interest was striatum
- Non-displaceable binding potential (BP_{ND})² of the PET-tracer was obtained by the two-parameter multilinear reference tissue model (MRTM2)³ using cerebellum as reference region
- Receptor occupancy (RO) was calculated using estimates of the non-displaceable binding potential at baseline (BP_{ND_0}) and post-treatment (BP_{ND_1}):

$$RO = \left(1 - \frac{BP_{ND_1}}{BP_{ND_0}}\right) \cdot 100\%$$

Modelling

The PK/PD (occupancy) relationship was analysed by E_{max} models using non-linear mixed effect modelling implemented in NONMEM 7.2.0.⁴ Three models were compared using the objective function value (OFV):

Model 1
$$RO = \frac{E_{max} \cdot (C_{parent} + \alpha \cdot C_{metabolite})}{EC_{50} + C_{parent} + \alpha \cdot C_{metabolite}}$$

Model 2
$$RO = \frac{E_{max} \cdot (C_{parent} + C_{metabolite})}{EC_{50} + C_{parent} + C_{metabolite}}$$

Model 3
$$RO = \frac{E_{max} \cdot C_{parent}}{EC_{50} + C_{parent}}$$

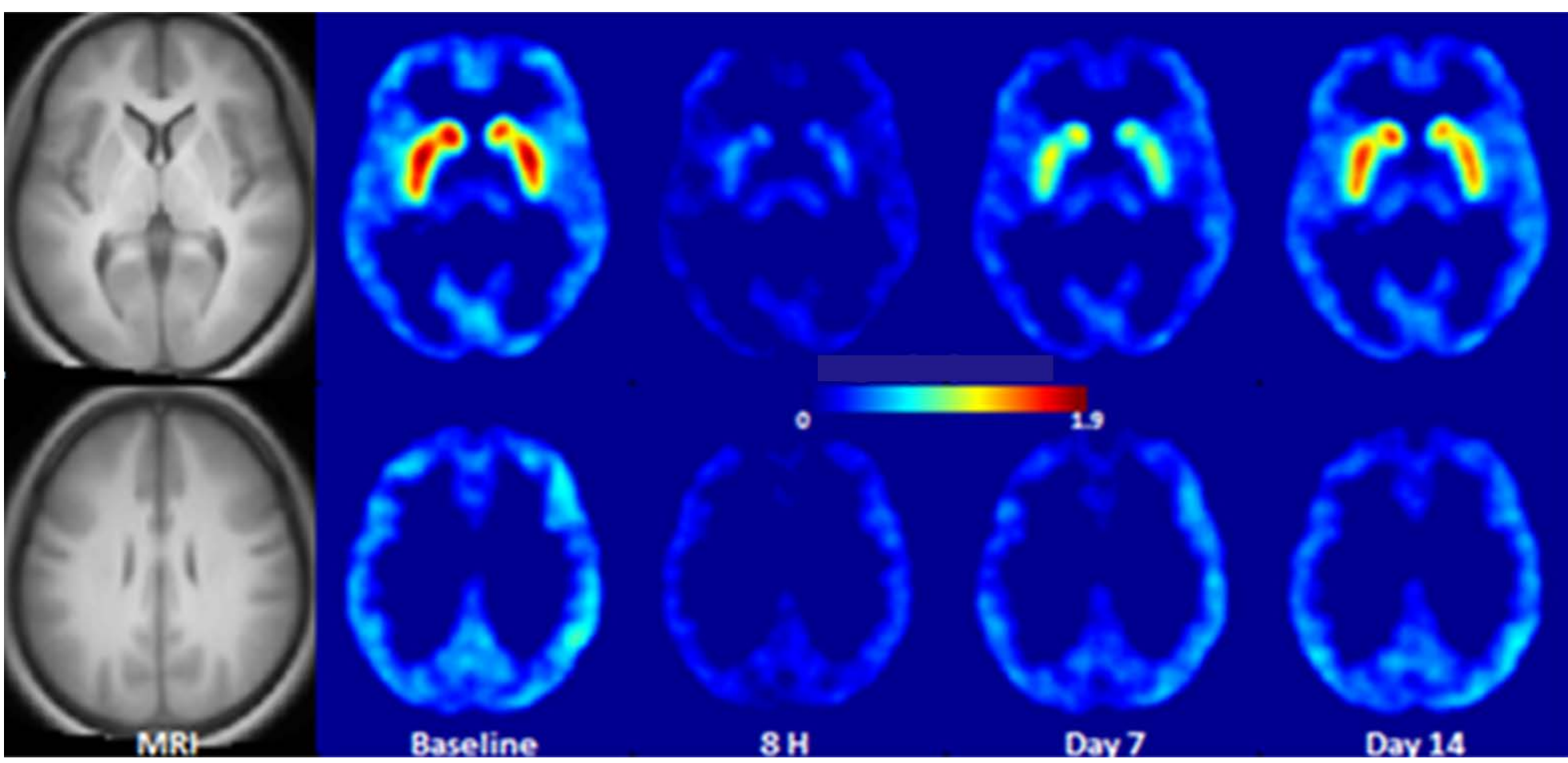
RO	Receptor occupancy
C_{parent}	Plasma concentration of parent compound
$C_{metabolite}$	Plasma concentration of metabolite
E_{max}	Maximum occupancy
EC_{50}	Plasma concentration at half of maximum occupancy
α	Non-negative factor of the relative receptor affinity of parent and metabolite

Models 1 and 2 and Models 1 and 3 are nested models. Proportional inter-individual variability (IIV) was included on EC_{50} . The residual variability (RV)/error model was additive.

Simulation

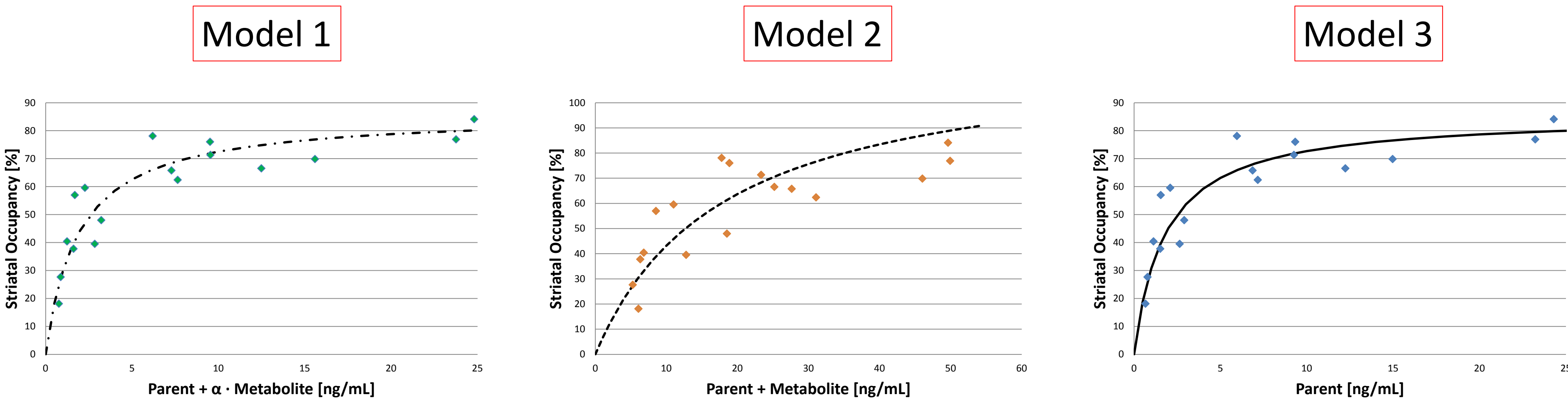
- The performance of the modelling approach was investigated using simulation
- Different receptor-drug systems with varying contributions/receptor affinities from the metabolite were simulated using the observed plasma concentrations and by varying the factor α
- $E_{max} = 100\%$
- $EC_{50} = 5$ ng/mL
- Affinity factor $\alpha = 0, 0.01, 0.1, 0.25, 0.5$, and 1
- IIV for EC_{50} and RV were set to the values obtained in Model 1 (same as in Model 3)

Imaging Results



Imaging From One Subject Parametric trans-axial images of BP_{ND} of the PET-tracer at baseline, and 8H, Day 7 and Day 14 post-dose scans (columns 2-5). Images in the upper row contain region of interest. MRI images are shown as reference (column 1).

Modelling Results



	Model 1	Model 2	Model 3
E_{max} [%]	86.2	121	85.7
EC_{50} [ng/mL] (IIV (%CV))	1.89 (35)	18 (36)	1.79 (35)
α	0.01	-	-
RV [%]	5.0	6.0	5.0
OFV	81.055	91.132	80.929

Simulation Results

- 6 data sets were generated with varying values of α
- Model 1 and Model 3 (both with E_{max} fixed to 100%) were run on all data sets.
- The analysis was capable of detecting relative receptor affinities above 0.1

True α	Model 1		Model 3		ΔOFV OFV(Model 1) - OFV(Model 3)
	EC_{50}	α	EC_{50}	α	
0	5.07	0.014	4.86		-0.07
0.01	5.09	0.025	4.71		-0.213
0.1	5.26	0.133	3.65		-3.076
0.25	5.5	0.319	2.62		-7.345
0.5	5.84	0.646	1.75		-10.662
1	6.33	1.32	1.04		-12.369

Conclusion

- The occupancy versus plasma concentrations data of the parent compound was adequately described by an E_{max} model
- PK/PD analysis showed no significant contribution from metabolite to the receptor occupancy
- Simulations supported that the modelling approach can identify contributions to receptor occupancy from the metabolite even at low relative affinities

Reference

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Acknowledgements

For performing the PET study:
Dr. Hiroto Kuwabara and Dr. Dean Wong
Johns Hopkins Medical Institutions