Integrated analysis of Human PET data across multiple brain regions and receptors to make inferences from limited data

Bart Laurijssens
Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Greenford UK

Introduction

The objective was to estimate the concentration – receptor occupancy relationship for the main target brain receptor (R1) for a centrally acting drug using human PET data. The drug also binds to a second receptor, R2, with lower affinity.

The data was limited in that for R1 maximal displacement was observed for all dose levels studied, and the extent displacement differed between two relevant brain regions.

2 Receptors – 3 Brain Regions

	Frontal Cortex	Putamen (striatum)	Caudate (striatum)
R1 receptor	N	Y	Y
R2 receptor	Y	N	N

- Both Radioligand and Drug have affinity for both receptors (drug: Kd R1 < Kd R2)
- Data is assumed to be at steady state (scans at wks 1,2,3,4 of repeat dosing)
- 8 subjects (3 scans per subject: baseline + 2 scans at ss)
- 3 dose levels: high (n=4), medium (n=2), and low (n=2). 10-fold range.

Method

For each brain region the model described the relationship between measured Volume of distribution ratio, VR, and drug concentration. The integrated model allowed certain parameters to be shared between the regions.

NONMEM was used for the analysis.

$$VR = (VR0 - 1) \cdot \left(1 - \frac{B\max \cdot Cave^{\gamma}}{IC50^{\gamma} + Cave^{\gamma}}\right) + 1$$

Since:

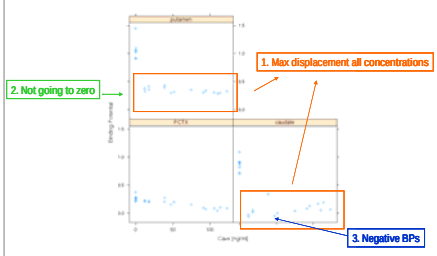
$$RO\% = 100 \cdot \frac{B\max \cdot Cave^{\gamma}}{IC50^{\gamma} + Cave^{\gamma}}$$

$$RO\% = 100 \times \frac{BP0 - BP}{BP0} \qquad BP = \frac{Vdt}{Vdr} - 1 = VR - 1$$

Where:

- **RO%**=receptor occupancy
- **Bmax=** maximum binding. In theory 1.
- **IC50=**concentration associated with 50% RO
- **gamma=**hill coefficient. In theory 1.
- **Cave=**average drug concentration during scan
- **BP=** Binding Potential (**BP0**, at baseline)
- **Vd=** Volume of Distribution (**Vdt** in area of interest, **Vdr** in reference region). Actual values not available.
- **VR**= Vd Ratio (**VD0**, at baseline)

The Issue



1. Cannot estimate IC50 R1 (main objective)
2. What explains difference Putamen – Caudate?
3. Therefore analysed VR instead of BP

Approach

1. Analyse all data together
2. Try different models that could explain the difference between Putamen and Caudate
3. Use confidence interval to get some estimate of IC50 for R1 (maximum likely value)

Possible explanations for Regional Difference

1. The radioligand binds to another specific site in the putamen. This binding cannot be displaced by drug: **Allow 0< Bmax Putamen <1**
2. Concentrations for drug are different in the putamen and the caudate: **Allow different IC50 for R1 in each region**
3. The putamen has both R1 and R2 (in a certain ratio). At concentrations studied, the R2 component has not been completely displaced yet: **Need BP0=FR*BP0R2 +(1-FR)*BP0R1 and each BP0 fraction to be displaced with its IC50 (R1 or R2)**

In the models the regions share: Emax=1 (unless specificied), IC50 for R1 and R2, gamma, BSV, residual error.

Results

Additional Binding site of radioligand best explains data in Putamen

Summary of the Model Develepment Sequence

PME run #	Model description	Objective Function	δOF[1]
2216	No BSV; gamma =1; putamen: IC50 different, Emax same	-228.116	28.779
2229	No BSV; gamma =1; putamen: 2 receptors, Emax same	-251.668	5.227
2127	BSV on VR0; gamma =1; putamen: IC50 same, Emax diff	-256.895	0
2189	No BSV; gamma =1; putamen: IC50 same, Emax diff	-256.895	-
2214	No BSV; gamma =1; putamen: IC50 diff, Emax diff	-256.917	-0.022

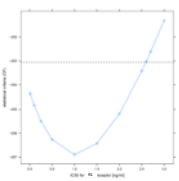
[1] Difference in Objective Function Relative to final model run 2189

Plasma IC50 for R1 estimated to be < 2.6 ng/ml

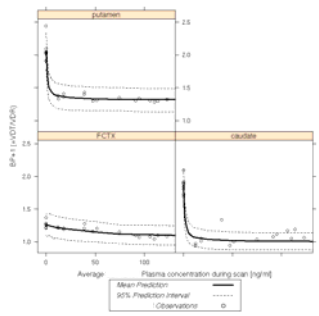
Population PK/PD parameters for Binding Potential in all 3 CNS regions simultaneously

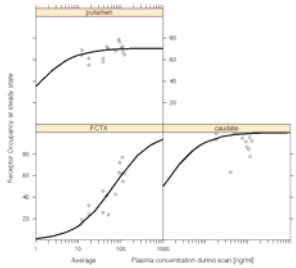
Parameter		Estimate	95% CI	Variability (%)
Fixed Effect Parameter				
θ_1	VR0 caud	1.86	(1.78,1.94)	
θ_2	VR0 put	2.06	(1.94,2.18)	
θ_3	VR0 ctx	1.26	(1.23, 1.29)	
θ_4	IC50 R2 (ng/mL)	67	(50, 84)	
θ_5	IC50 R1 (ng/mL) (1)	1.0	(? , 2.6)	
θ_6	Emax put	0.71	(0.64, 0.77)	
θ_7	Gamma	1 fixed		
Random Effect Parameter				
σ^2	Proportional residual error	0.0048		6.9

Data Source: appendix 1
(1) 95% confidence interval determined by profiling

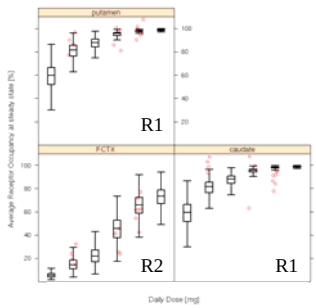


In Pictures





The highest dose in the clinic was predicted to give > 90% R1 RO in 97.5% of subjects, and an average of about 65% R2 RO



Conclusions

- Despite the data the IC50 for R1 could be estimated to be < 2.6 ng/ml. This allowed us to predict minimal RO for doses in the clinic.
- The IC50 for R2 was estimated to be (95% CI) = 69 (55, 90) ng/ml.
- The analysis also suggested about 29% unexplained non-specific binding of the radioligand in the Putamen

Acknowledgements

Thanks to the study team members and our colleagues at the Clinical Imaging Centre at Imperial College in London: John Tonkyn, Maria Davy, Nicola Thomas, Christine Parker, Vin Cunningham and Ilan Rabiner, as well as Stefano Zamuner