

Improved dose selection for PET occupancy studies

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Objectives

Receptor occupancy can be assessed by Positron Emission Tomography (PET). Since PET measurements are costly it is important to ensure that the study is optimized to provide sufficient information based on few experiments. Generally, doses targeting 50% occupancy is perceived as most informative when estimating the relationship between exposure and occupancy.

The objective of the present work was to investigate how the doses should be allocated in order to maximize the precision of the derived relationship between exposure and receptor occupancy and to investigate how the optimal dose allocation depends on distribution of specific uptake in the brain.

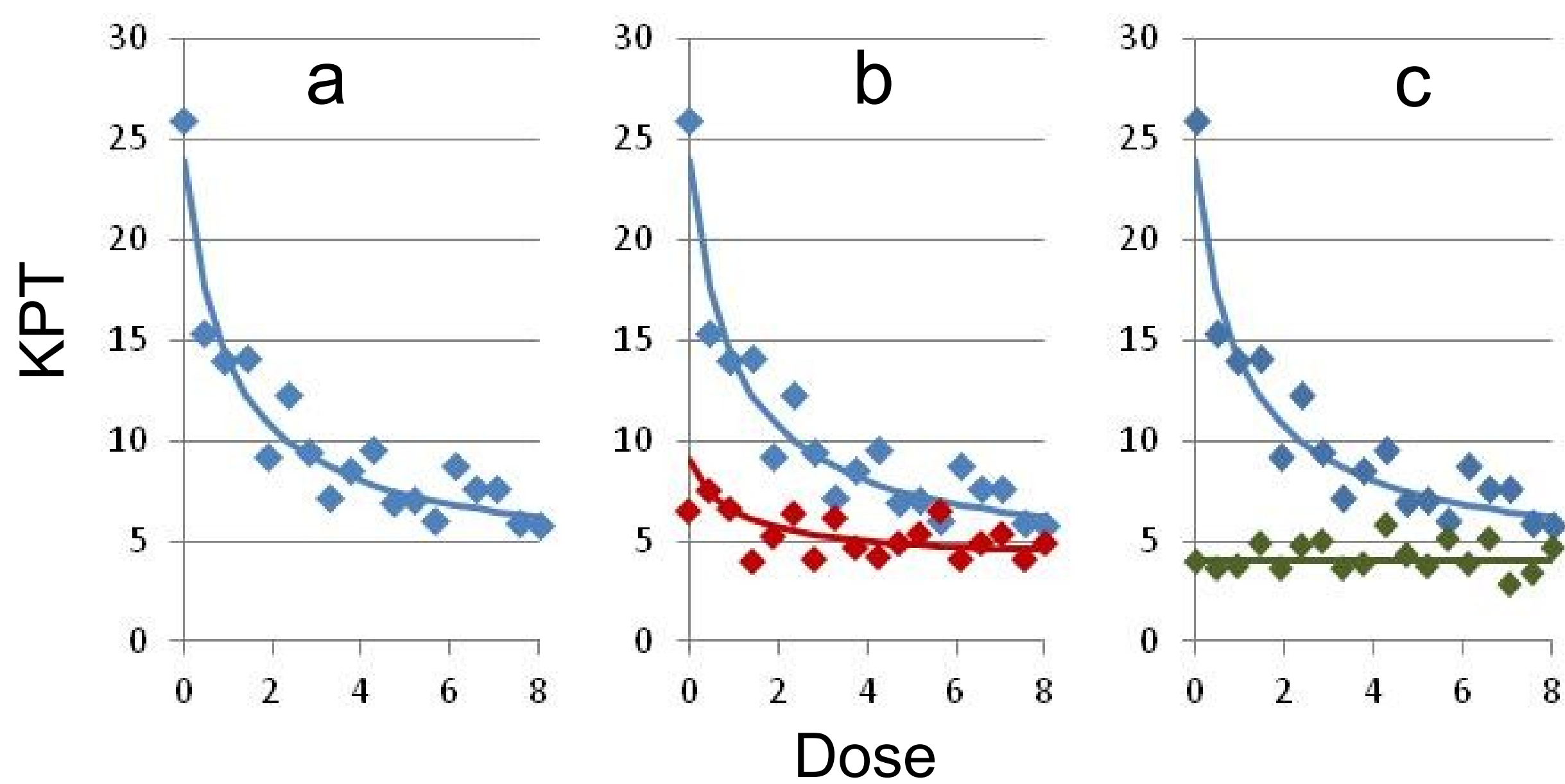
Methods

Based on each PET-measurement, the partition coefficient, brain/plasma (K_{Pt}) can be derived for each region. Displacement of the radioligand from the receptor by a drug competing for the same binding site will result in a reduced K_{Pt}. The relationship between K_{Pt} and dose can be estimated by a saturation function (EQ1) where the specific uptake (K_{PS}), the non-displaceable uptake (K_{PND}) and the affinity (ID₅₀) are estimated. The occupancy can then be derived from the dose and the estimated value of ID₅₀. The study design considered included 6 volunteers with three PET-measurements in each volunteer of which at least one had to be at a dose of zero.

EQ 1: $K_{Pt} (obs) = (K_{PS} * (1 - (Dose / (Dose + ID_{50}))) + K_{PND}) * (1 + eps)$

The situations considered in the analysis of the data are illustrated in Figure 1

Fig 1 Simulated dose response from model



- a) A single region of interest is included.
- b) Two regions with different receptor densities (K_{PS}) are included.
- c) Two regions are included, where one is a reference region, known to be void of receptors (K_{PS} fixed to 0)

In addition, the effect of additive residual error was investigated. The D-optimal design criterion was compared to D_s with ID₅₀ as the parameter of interest. Also the situation in which tolerability limits the possibility to fully saturate the binding was investigated. The assumed value of ID₅₀ was 1. The optimal dose allocation was estimated using the optimal design tool PopED [1].

Results

If a reference region exists the precision of the ID₅₀ is less sensitive to the selected doses and no high dose with full saturation is needed. If no reference region exists, doses that result in close to full saturation improve the precision of the ID₅₀ estimate. When only a single region is included, near full saturation measurements are essential. With proportional residual error the optimal doses are higher compared to an additive residual error. D_s-optimal designs include more doses near the ID₅₀ value as compared to D-optimal designs.

a) A single region				
Model description	Residual error	Criteria	Optimal doses (n x dose)	CV% (ID ₅₀)
Base case *	Proportional	D _s	6x0, 9x1.44, 3x8	27%
D-optimal	Proportional	D	6x0, 6x1.44, 6x8	30%
Additive error	Additive (SD=0.4)	D _s	6x0, 8x0.8, 4x8	5%
Max dose= 1.5 (60% occupancy)	Proportional	D _s	6x0, 8x0.54, 4x1.5	78%

b) Two regions with different receptor densities (K _{PS})				
Model description	Residual error	Criteria	Optimal doses	CV% (ID ₅₀)
Base case *	Proportional	D _s	6x0, 8x1.8, 4x8	21%
D-optimal	Proportional	D	9x0, 4x1.8, 5x8	23%
Additive error	Additive (SD=0.4)	D _s	6x0, 1x0.8, 8x0.96, 3x8	4%
Max dose= 1.5 (60% occupancy)	Proportional	D _s	0x8, 10x1.5	26%

c) Two regions where one is void of receptors				
Model descr	Residual error	Criteria	Optimal doses	CV% (ID ₅₀)
Base case *	Proportional	D _s	7x0, 11x3.2.	16%
D-optimal	Proportional	D	9x0, 9x2.4	17%
Additive error	Additive (SD=0.4)	D _s	6x0, 11x1.1, 1x1.3	3%
Max dose= 1.5 (60% occupancy)	Proportional	D _s	0x8, 10*1.5	18%

* Base case: D_s-optimal, Max dose=8 (89% occupancy), prop error (CV=17%)

Discussion and Conclusions

The optimal dose allocation depends on assumptions regarding nonspecific brain uptake, distribution of receptors in the brain and the residual error. Targeting an occupancy of 50% is not always most informative for the estimation of the relationship between exposure and occupancy. D_s-optimal design provides a mean to focus on the parameter of interest in the model.

References

[1] PopED: An extended, parallelized, nonlinear mixed effects models optimal design tool, Joakim Nyberg, Sebastian Ueckert, Eric Strömberg, Stefanie Hennig, Mats O. Karlsson, Andrew C. Hooker, computer methods and programs in biomedicine, 2012.