Using PET total volume of distribution (V_T) in estimating the PK-RO relationship in the absence of reference regions.

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Introduction

In a Positron Emission Tomography (PET) study, receptor occupancy (RO) can be obtained from the fractional decrease in the volume of distribution of the specifically bound radioligand (V_S)[1]. V_S can be derived from V_T (total volume of distribution) and V_{ND} (non-displaceable radioligand) which is generally measured directly from reference regions.
In the absence of reference regions, RO values and V_{ND} can be estimated by linear regression using volume of distribution at baseline (V_{T0}) and after drug administration (V_T) [2].

Objectives

- To apply a population approach using V_T values in a PET study in order to estimate the PK-RO relationship.
- To compare the proposed approach to the conventional one which uses the derived RO values.

Methods

Data

- Data from a neuroreceptor drug occupancy study. Range of single doses tested to characterize the PK-RO relationship.
- PET scans at baseline, tmax and 24h post dose.
- PK profiles measured after each dose. Calculation of C_{ave} (average concentration during the PET scan) as a mean between pre scan and post scan concentrations.

Models

A population modelling approach was applied for both V_T and derived RO values in NONMEM V.

Model assumptions:

- direct C_{ave}-RO relationship (indirect model explored but limited data),
- slope fixed to 1 on theoretical grounds,
- V_{T0} constant over the time,
- same RO and V_{ND} over the brain regions.

V_T model

V_T values from the PET study were simultaneously fitted using the equation based on the Emax model:

$$V_{Tij} = V_{T0ij} - \left(\frac{C_{ave\,i}}{EC_{50\,i} + C_{ave\,i}}\right) \times \left(V_{T0ij} - V_{NDi}\right)$$

where i is a subject, j is a brain region, V_{Tij} is the measured PET volume of distribution, C_{avei} is the average concentration during the PET scan.

- EC_{50i}, V_{T0ij} and V_{NDi} were estimated using a population approach including all the brain regions.
- Proportional inter-subject variability and residual error were preferred.
- RO values were calculated from the individual V_{Tij}, V_{T0ij} and V_{NDi} using the V_T model above.

RO model

Derived RO values were described by an Emax model:

$$RO_i = \frac{E\max \times C_{ave\,i}}{EC_{50\,i} + C_{ave\,i}}$$

where i is a subject, RO_i is the receptor occupancy value derived by linear regression, C_{avei} is the average concentration during the PET scan, EC_{50i} is estimated and Emax is fixed to 100%.

The following residual error models were tested:

- proportional error model,
- additive error model,
- a model derived from the propagation of the error applied to V_T observations, in this case the variance can be described as:

$$\sigma^2_{RO} = \sigma^2 (100 - RO)^2$$

where σ is derived assuming a proportional error model on the volume of distribution observations (Appendix).

Model evaluation

- To characterize V_T model performance:
Visual predictive check (VPC) of V_T as a function of C_{ave} per brain region.
- To compare PK-RO profiles across different models:
VPC of RO as a function of C_{ave} where RO values are
i) derived by linear regression and the RO model or
ii) calculated from the V_T model.

Results

Data description

- 3 doses investigated: 6ug, 14ug and 120ug.
- 11 C_{ave} calculated from the plasma concentrations.
- 17 PET scan measurements: 6 at baseline, 6 at tmax (3h post dose) and 5 at t24 (24h post dose).
- For each scan, V_T measured across 12 brain regions.

PKPD population estimates

	V_T model [1]	RO models		
		Propagation error	Proportional error	Additive error
EC_{50} ng/mL CV (%)	0.007 30%	0.007 29%	0.004 14%	0.005 19%
Ω EC_{50} CV (%)	44 % 76%	55% 35%	ND	ND
Res. error CV (%)	12% 11%	32% 25%	18.5% 43%	12.5 19%

[1] = Typical values and variances of V_{T0ij} per brain region and V_{NDi} were well estimated (CV <20%)
ND= Not Determinable

- Similar EC_{50} between V_T model and RO model with propagation error. Smaller EC_{50} estimates provided by RO models with proportional and additive errors.
- Inter-subject variability on EC_{50} estimated only using V_T model and RO model with propagation error.
- Residual error values smaller for the V_T values than for the RO values.

Diagnosis plots for the V_T model

Goodness of fit plots

Based on the plots below, satisfactory prediction of the V_T model.

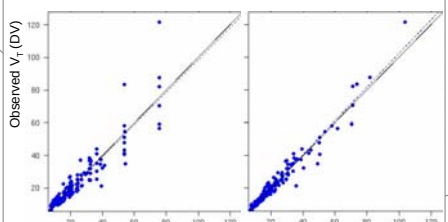

Figure 1. *V_T observed versus PRED and IPRED*

Visual Predictive Check

VPC in each brain region: observations well distributed around the median and satisfactory overall variability. VPC for two regions reported in Figure 2.

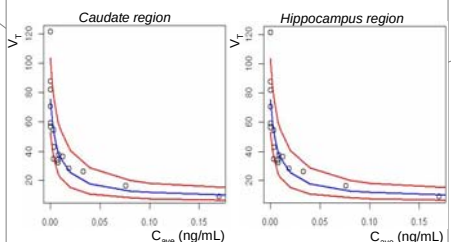

Figure 2. *VPC of V_T for Caudate and Hippocampus brain regions*
Dots = observed V_T in a brain region, blue line = model predicted V_T median, red line = 5th and 95th percentile

VPC of RO across models

- Satisfactory VPC using V_T values or using RO values with an error propagation model.
- Proportional and additive error models on RO values inflated the overall variability.

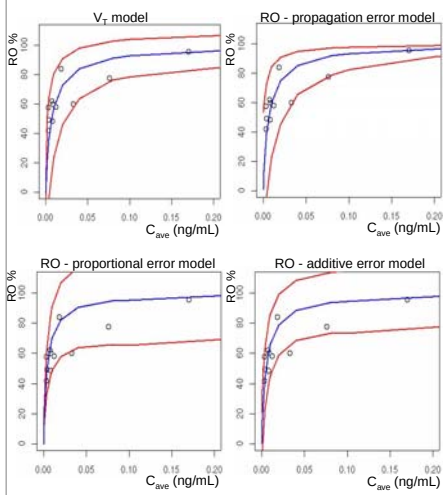

Figure 3. *VPC of RO as a function of C_{ave} for the different models*

Conclusions

- A population modelling approach was proposed to characterize the PK-RO relationship in PET studies using the PET total distribution volume (V_T) when no reference region exists.
- Model using V_T values provided additional information on V_{T0ij}, V_{NDi} as well as robust estimates of EC_{50i}, inter-subject variability and residual variability.
- Consistent results in terms of typical value of EC_{50}, inter-subject variability and VPC were obtained between the approach using V_T values and RO values with a propagation error model.
- The proportional and additive error models inflated variability at high RO values and should not be considered for simulation purposes (e.g, simulations at steady state).
- Although a clear benefit of the V_T model versus all the RO models was not shown in this PET study, we believe that the V_T model would provide more robust estimates in the case of a drug with a complex mechanism of action (eg. indirect response).

Appendix

Propagation Error Model

$$RO = f(VT, VT_0) = \frac{VT_0 - VT}{VT_0 - V_{ND}} = 1 - \frac{BP}{BP_0}$$

where BP_0 and BP is the binding potential at baseline and after treatment, respectively.

Assuming a proportional error on the observations (σ_{BP}=BP* σ) and using the propagation of the error formula, RO variance can be described as:

$$\sigma^2_{RO} = \left(\frac{\partial f}{\partial BP}\sigma_{BP}\right)^2 + \left(\frac{\partial f}{\partial BP_0}\sigma_{BP_0}\right)^2 = \frac{1}{BP_0^2}\sigma^2_{BP} + \left(\frac{BP}{BP_0^2}\right)^2 \sigma^2_{BP_0}$$

$$\sigma^2_{RO} = \frac{1}{BP_0^2}\sigma^2 \cdot BP^2 + \left(\frac{BP}{BP_0^2}\right)^2 \sigma^2 \cdot BP_0^2 = 2 \cdot \frac{BP^2}{BP_0^2}\sigma^2 = 2\sigma^2(1 - RO)^2$$

References

- [1] Lammertsma et al. JCBFM 11:545-556, 1991.
- [2] Lassen et al. JCBFM 15:152-65, 1995.