Simulation to compare the reference tissue models in [^{11}C]Carfentanil bolus studies

Materials and methods

Study material consists of four pilot PET studies uf0498 and uf0499 for subject #1, and uf0504 and uf0505 for subject #2. Blood and plasma data and metabolite fractions were measured. The metabolite corrected plasma curves and total blood curves from each study are shown in Fig. 1. For simulations, the blood and plasma curves were interpolated to same sampling times and averaged (Fig. 2).

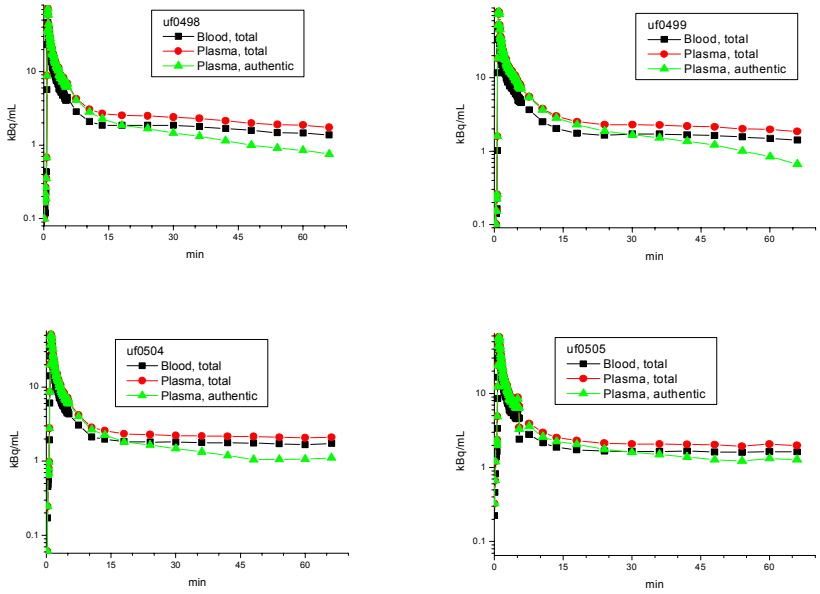


Figure 1. Total radioactivity concentration in blood and plasma, and metabolite corrected radioactivity concentration in plasma. Notice logarithmic scale in radioactivity concentration.

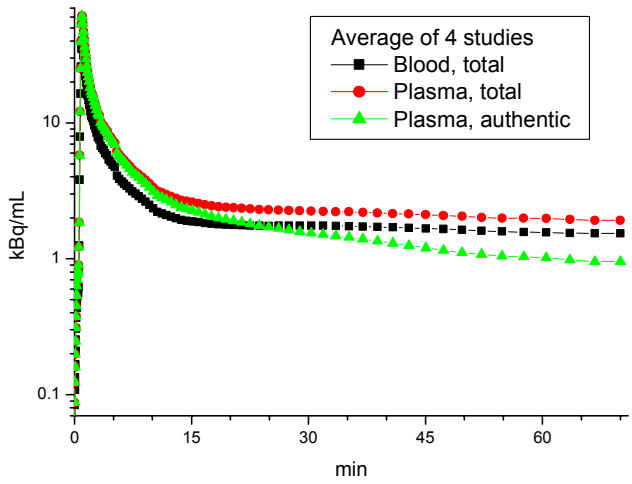


Figure 2. Average radioactivity concentration in blood and plasma. These time-activity curves are used in the simulations.

Simulations are based on the traditional three-tissue compartmental model and model parameter values, estimated from measured [^{11}C]carfentanil PET data for occipital cortex (reference region), frontal cortex and thalamus, as presented by Frost et al. (1989); frontal cortex and thalamus were selected to represent low and high binding brain regions. The simulation parameter values are shown in Table 1; in the present study the 25-75% occupance is simulated by decreasing the binding potential ($BP=k_3/k_4$) by 25-75%. In addition, in the simulations the blood flow is estimated to be 80 mL·(min·100 mL)$^{-1}$, blood volume 4.5% and the fraction of arterial volume 30% [Ito et al., 2001].

Table 1. Rate constants (1/min) used in the simulations.

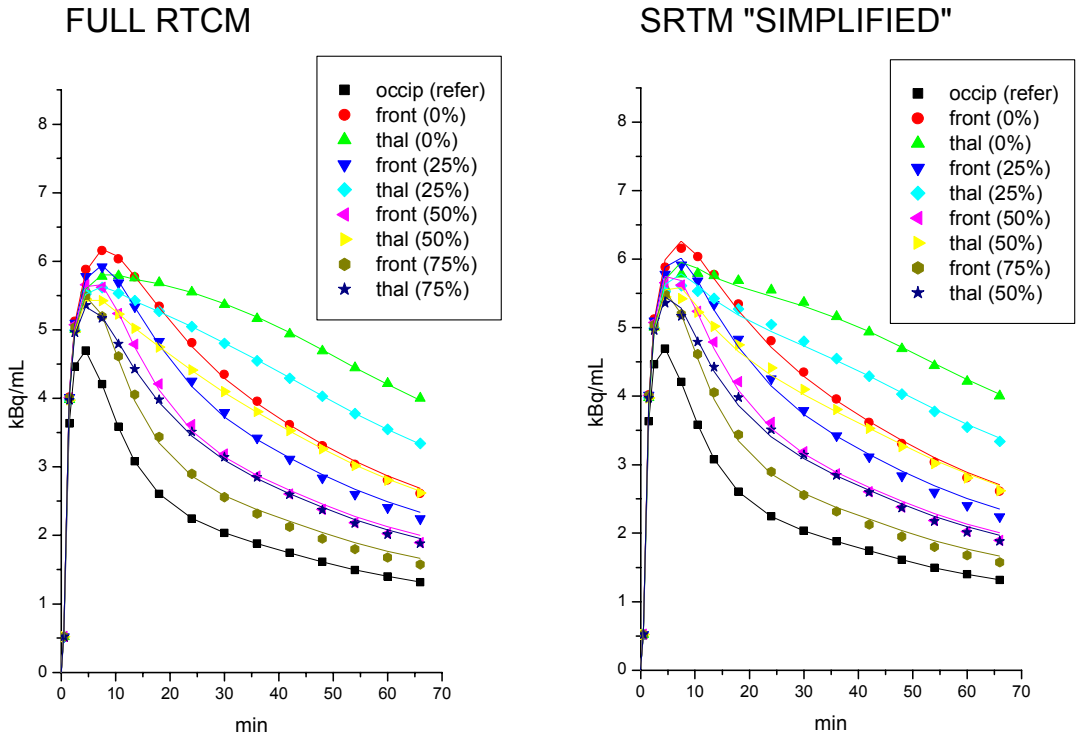
	Control study			25% occupance		50% occupance		75% occupance	
	Occip	Front	Thal	Front	Thal	Front	Thal	Front	Thal
K_1	0.094	0.108	0.107	0.108	0.107	0.108	0.107	0.108	0.107
k_2	0.173	0.201	0.201	0.201	0.201	0.201	0.201	0.201	0.201
k_3	0	0.382	0.201	0.3343	0.1759	0.2865	0.1510	0.2388	0.1256
k_4	0	0.217	0.060	0.2533	0.0700	0.3256	0.0900	0.5426	0.1500
k_5	0.029	0.029	0.029	0.029	0.029	0.029	0.029	0.029	0.029
k_6	0.036	0.036	0.036	0.036	0.036	0.036	0.036	0.036	0.036
k_3/k_4	0	1.760	3.350	1.320	2.5125	0.880	1.675	0.440	0.8375

Simulated tissue curves were fitted using three calculation models applying reference input instead of plasma: (original) reference tissue model [Blomqvist et al., 1989; Cunningham et al., 1991], simplified reference tissue model [Lammertsma and Hume, 1996], and Logan plot analysis [Logan et al., 1996] with simulated occipital cortex curve as a reference curve. The reference tissue models provide estimates of BP, and the Logan plot an estimate of DVR-1, which all are assumed to represent the binding potential, or k_3/k_4. Occupance values were calculated from those parameter estimates, similarly as in actual PET studies, and binding potentials and occupances were compared to the ones used to simulate the tissue curves. Simplified reference tissue model and Logan plot analysis, but not the original reference tissue model, can be applied pixel-to-pixel to produce parametric images of binding potential.

For simulated data, times between 30 and 70 min were used to fit a straight line to the Logan plot.

Results and discussion

The simulated tissue curves and curves fitted to the original and simplified reference tissue model are shown in Figures 3a and 3b. Figure 3c contains the Logan plots. The BP and DVR-1 results from these analyses and the occupance values calculated from those are listed on Tables 2a, 2b and 2c. All calculation models gave essentially similar results. The fits were not perfect, and the most important parameters representing the binding, BP and DVR-1, were underestimated by about 50%. However, the underestimation did not change much between high and low binding regions or during high or low receptor occupancy. This lead to occupance values that were very close to the correct values, because the most important errors (e.g. non-specific binding, causing the underestimation of binding in these simulations) are cancelled out in calculation of the occupance.



Figures 3a and 3b. Simulated tissue time-activity curves (symbols) and the corresponding fitted curves (lines) from the original (a) and simplified (b) reference tissue model on different receptor occupance levels.

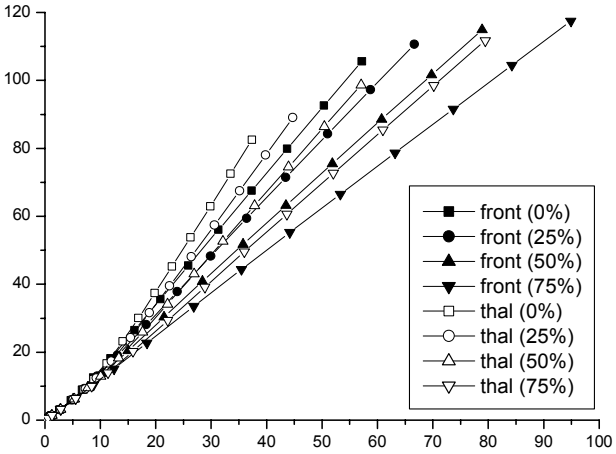


Figure 3c. Logan plots calculated from the simulated curves for fontal cortex, thalamus and occipital cortex (reference region) on different recepor occupance levels.

Table 2a. Parameters estimated from the simulated tissue curves applying the original reference tissue model.

	Control study			25% occupance		50% occupance		75% occupance	
	Occip	Front	Thal	Front	Thal	Front	Thal	Front	Thal
R_1	-	1.116	1.010	1.120	1.101	1.122	1.108	1.116	1.114
k_2	-	0.299	0.150	0.355	0.167	0.417	0.213	0.500	0.306
k_3	-	0.263	0.267	0.210	0.204	0.182	0.140	0.211	0.102
k_3/k_4	-	0.9322	1.6026	0.7117	1.2349	0.4863	0.8502	0.2550	0.441
Bias	-	-47%	-52%	-46%	-51%	-45%	-49%	-42%	-47%
Occup	-	-	-	23.7%	22.9%	47.8%	46.9%	72.6%	72.5%
Bias	-	-	-	-5.4%	-8.2%	-4.3%	-6.1%	-3.1%	-3.4%

Table 2b. Parameters estimated from the simulated tissue curves applying the simplified reference tissue model.

	Control study			25% occupance		50% occupance		75% occupance	
	Occip	Front	Thal	Front	Thal	Front	Thal	Front	Thal
R_1	-	1.018	1.008	1.026	1.014	1.040	1.023	1.065	1.043
k_2	-	0.197	0.110	0.212	0.112	0.243	0.120	0.353	0.154
k_3/k_4	-	0.9397	1.6442	0.7174	1.2670	0.4895	0.8693	0.2555	0.4456
Bias	-	-47%	-51%	-46%	-50%	-44%	-48%	-42%	-47%
Occup	-	-	-	23.7%	22.9%	47.9%	47.1%	72.8%	72.9%
Bias	-	-	-	-5.4%	-8.2%	-4.2%	-5.7%	-2.9%	-2.8%

Table 2c. Results of Logan plot analysis applied to the simulated tissue curves.

	Control study			25% occupance		50% occupance		75% occupance	
	Occip	Front	Thal	Front	Thal	Front	Thal	Front	Thal
DVR-1	-	0.93	1.56	0.70	1.22	0.47	0.85	0.23	0.43
Bias	-	-47%	-53%	-47%	-51%	-47%	-49%	-48%	-49%
Occup	-	-	-	24.7%	21.8%	49.5%	45.5%	75.3%	72.4%
Bias	-	-	-	-1.1%	-12.8%	-1.1%	-9.0%	+0.4%	-3.4%

Simplified reference tissue model and Logan plot analysis seem to provide accurate receptor occupance values, and are thus recommended for analysis of [^{11}C]carfentanil studies without blood sampling. Original reference tissue model does not give better results than the simplified version. If quantitative binding potential values are required in addition to the occupances, a full kinetic modelling with blood sampling will be needed. Based on these simulations, the simplified reference tissue model is recommended over Logan plot, because it shows similar biases in occupance values in all situations. The effect of measurement noise was not simulated; in case of noisy data, different analysis methods may behave differently.

References:

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