Application of Simcyp® simulator platform for the assessment of the pharmacokinetic profile of Gd-DOTA regarding its disposition in brain tumor lesions with different vasculature

Marios Spanakis[1], Vangelis Sakkalis[1], Kostas Marias[1]

[1]Computational Bio-Medicine Laboratory, Institute of Computer Science, Foundation for Research and Technology - Hellas, Heraklion, Crete, Greece

marspan, sakkalis, kmarias @ ics.forth.gr

Objectives: Gadolinium based contrast agents (GBCA) are used in dynamic –contrast enhanced magnetic resonance imaging (DCE-MRI) for diagnosis of lesions such as brain tumors with implementation of pharmacokinetic analysis for quantification of the vessel leakage of tumor's abnormal vasculature (Figure 1) [1]. The aim of this work was to assess through physiologically-based pharmacokinetic modeling (PBPK) the impact of different fraction of vasculature of a brain tumor on the PK profile of Gd-DOTA (gadoteric acid, DOTAREM®).

Methods: The PK profiles were generated through whole body-PBPK models and *in silico* clinical trials with Simcyp® simulator platform [2]. The typically administered dose (i.v., 0.1 mmol/kg) was simulated for the estimation of tracer's concentration for up to 15 minutes post administration in order to be in line with the typical DCE-MRI clinical setting. The brain tumor lesion (BTL) compartment was introduced as an additional organ in the simulator with tissue characteristics modified to fit those of brain and brain tumors. Keeping all parameters constant for BTL (size, composition) and the same virtual profile, simulations run modulating each time the proportion of capillary bed in the BTL (0.01-10% of the total tissue) (Table 1 & 2).

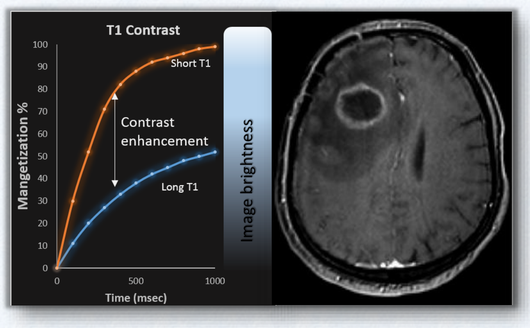


Figure 1. A brief description of the mechanism for DCE-MRI and GBCA: Magnetic resonance imaging (MRI) uses the resonance of the protons to generate images. Spin–lattice relaxation is the mechanism by which the z component (in x,y,z graph) of the magnetization vector comes into thermodynamic equilibrium with its surroundings (the "lattice") in MRI. The rate at which the longitudinal Mz component of the magnetization vector recovers exponentially towards its thermodynamic equilibrium is characterized by Spin–lattice relaxation time (T1). Water protons in different tissues have different T1 values. Furthermore T1 is significantly different between grey matter and white matter which is further exploited to reproduce from signal the organ anatomy (i.e. brain). Gd-based contrast agents due to their paramagnetic properties shorten the T1 relaxation times of atoms within body tissues after intravenous injection thus enhancing the contrast of the acquired MRI image.

Table 1. Demographic and physiology data of the representative individual.

Gender	Age (Years)	Weight (kg)	Height (cm)	Brain Weight (g)	Cardiac Output (L/h)	Haematocrit (%)	Renal Function
M	23	81	177	1391.52	355.64	43.00	1.13

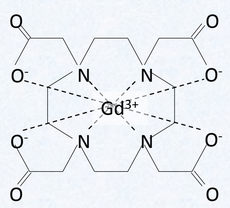


Figure 2. Chemical structure of Gd-DOTA (gadoteric acid, DOTAREM®).

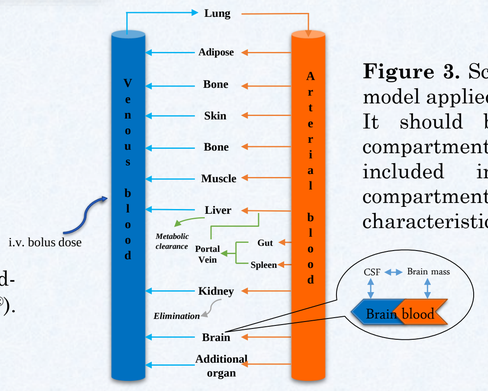


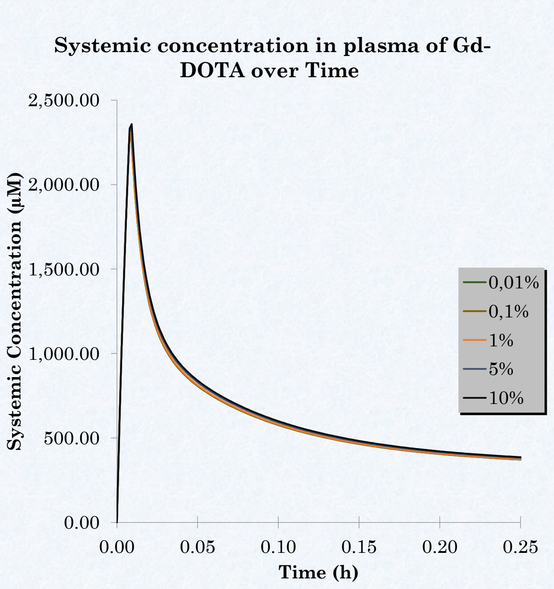
Figure 3. Schematic representation of a whole-body PBPK model applied in Simcyp® simulator platform for this study. It should be noted that for the brain three sub-compartments are applied with BBB permeability to be included in algorithms. The "Additional organ" compartment was used to simulate the brain tumor lesion characteristics.

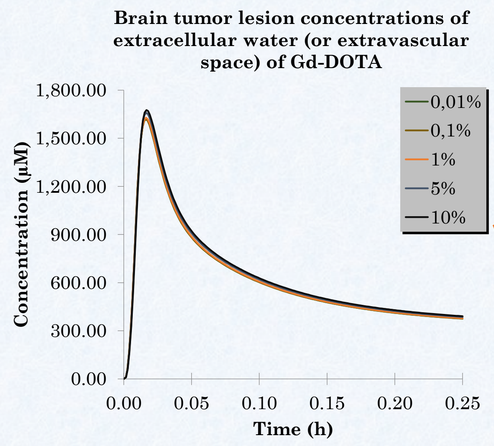
Table 2. Physicochemical and pharmacokinetic parameters introduced in the Simcyp® platform for the study design along with additional organ characteristics for the simulation of the brain tumor lesion

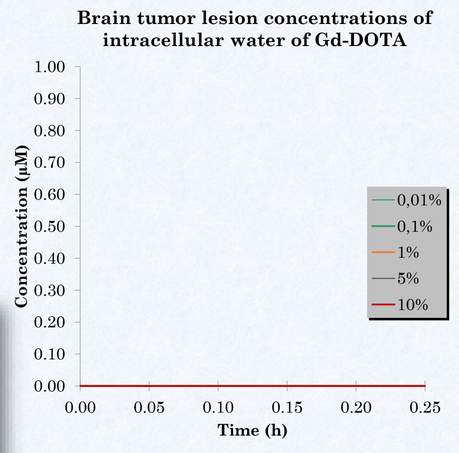
Physicochemical properties	
Molecular Weight (g/mol)	558,64
pKa (acid)	0,10
pKa (base)	9.59
logP	-2,90
fu	1,00
Pharmacokinetic properties	
CL (L/h)	6,0
Vd L/Kg	0,21
Route of elimination	Renal elimination
Study design	
Dose (i.v)	0.1 mmol/kg (55.86 mg/kg)
Study duration	15 min
Distribution model	Full-PBPK
BBB passive permeability	$1,4*10^{-7}$ (L/h) (predicted)
Virtual profiles simulated	Virtual representative of oncology population* [4]
Brain tumor lesion characteristics	
BTL : Extracellular Water (%)	9,20
BTL: Intracellular Water (%)	67,80
BTL: Neural Lipids (%)	5,10
BTL: Neutral Phospholipids (%)	5,65
BTL: AP (mg/g)	0,40
BTL pH : EW	7,40
BTL pH : IW	7,00
BTL: Male (% of Qc)	0,65
BTL % of Body Weight	0,01
BTL tissue Density (g/L)	1300,00
BTL Capillary Bed (%)	0,01-10,00

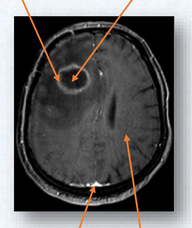
** The virtual representative is based on the work of Cheeti S, Budha NR, Rajan S, Dresser MJ, Jin JY. (2013) A physiologically based pharmacokinetic (PBPK) approach to evaluate pharmacokinetics in patients with cancer. Biopharm Drug Dispos.34(3):141-54.*

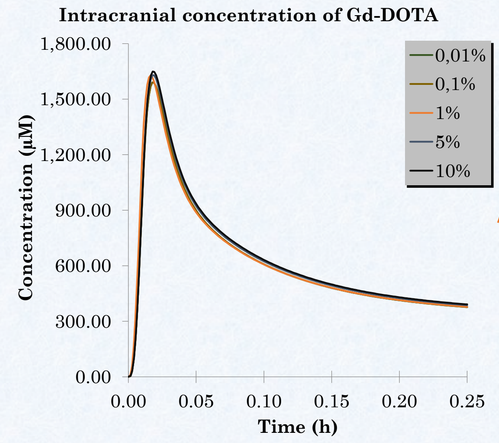
Results: The results from the simulations for Gd-DOTA estimate a mean systemic plasma concentration C_{max}=2.3 mM, a mean AUC =163.16 μM.h and clearance CL= 5.6 L/h. The mean $C_{max,int}$ of intracranial blood was 1.6 mM with an AUC=159.73 μM.h. Regarding BTL, the maximum extravascular concentrations of Gd-DOTA ranged from 1.6-1.7 mM following the BTL's increased vasculature. Taken into consideration blood brain barrier permeability, Simcyp® predicted a zero concentration-time profile for the brain mass revealing the impact of BBB regarding tracer's limited disposition in the brain as it is observed in clinical settings of DCE-MRI (Table 3 & c-t graphs)











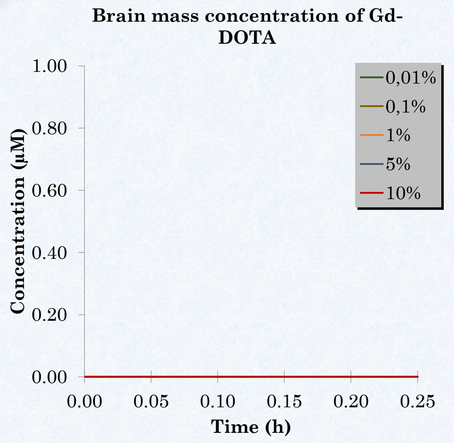


Table 3. Predicted PK parameters of Gd-DTPA from Simcyp® in systemic circulation, intracranial blood and extracellular (or extravascular) space of different vascularity in the simulated BTL

BTL vascularity	BTL 10%		BTL 5%		BTL 1%		BTL 0.1%		BTL 0.01%	
PK parameters	**Cmax μM**	**AUC μM*h**	**Cmax μM**	**AUC μM*h**	**Cmax μM**	**AUC μM*h**	**Cmax μM**	**AUC μM*h**	**Cmax μM**	**AUC μM*h**
Body	2358,54	167,06	2337,10	165,04	2302,89	161,85	2293,40	160,97	2292,43	160,88
Brain	1649,51	163,54	1630,10	161,57	1624,59	158,45	1614,20	157,59	1601,83	157,50
Simulated BTL	1676,11	164,17	1638,51	161,40	1628,57	160,86	1620,19	160,16	1619,33	159,22

Conclusions: The results of the PBPK approach through the application of Simcyp® reveal a suitable method to describe *in silico* the impact of different vasculature of a brain tumor on tracer's PK profile. The evaluation of tracer kinetics through *in silico* clinical trials and PBPK models represent novel approaches for DCE-MRI in population and/or individual level [3,4]. This methodology shows potentials on the possible coupling of the results with studies correlating image analysis with tumor growth models regarding the estimation of GBCA profiles in different population cohorts.

References

1) Koh TS, Bisdas S, Koh DM, Thng CH (2011) Fundamentals of tracer kinetics for dynamic contrast-enhanced MRI. Journal of magnetic resonance imaging : JMRI 34 (6)

2) Jamei M, Marciniak S, Feng K, Barnett A, Tucker G, Rostami-Hodjegan A (2009)."The Simcyp population-based ADME simulator." Expert Opin Drug Metab Toxicol 5(2): 211-23.

3) Spanakis M, Marias K. (2014) "In silico evaluation of gadofosveset pharmacokinetics in different population groups using the Simcyp® simulator platform" In Silico Pharmacology, 2:2

4) Spanakis M, Oraiopoulou ME, Tzamali E, Sakkalis V, Maris TG, Papadaki E, Karantanas A, Marias K (2014)"An in silico estimation of the pharmacokinetic profile and the disposition of Gd-DTPA in brain tumor lesions of different vasculature through PBPK models". European Association of Neuro-Oncology, Turin, Italy; 10/2014