Comparative analysis of Gd vs Dy in DSC-MRI studies of a high grade glioma murine model

R. Pérez-Carro[1], J. Pacheco-Torres[1], S. Cerdán[1], and P. Lopez-Larrubia[1]
[1]Insituto de Investigaciones Biomedicas, CSIC/UAM, Madrid, Spain

Introduction

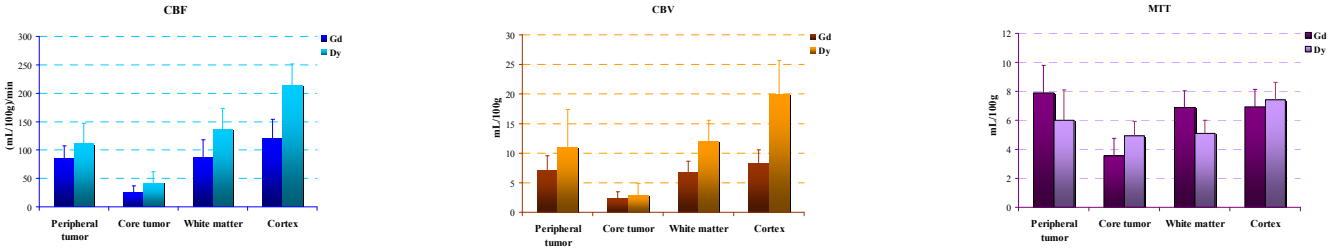
Present methods to image microvascular flow involve mainly the intravenous administration of a bolus injection from a paramagnetic contrast followed by the rapid, time-resolved, MR imaging of the kinetics of its first pass through the microvasculature of the imaged slice [1,2]. This approach relies both on the chemical nature of the contrast agent used and on the inherent properties of the MR technique implemented. Most protocols combine the use of conventional contrast agents as Gd(III)DTPA (Bayer-Schering, Berlin, DE) or Gd(III)DOTA (Guerbet, Paris, FR, Bracco, Torino, IT) and rapid Echo Planar MR imaging methods to resolve in time the transit of the bolus of contrast agent through the imaging slice. In the case of the brain, analysis of the kinetic curves allows for the determination of the blood volume (CBV), blood flow (CBF), mean transit time (MTT) and eventually capillary permeability[3]. In this line Dy-complexes have been proposed to measure cerebral blood volume and to delineate healthy and damaged tissues by MRI[4]. On the other hand, dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) has already proven to be of clinical value, in order to distinguish between different tumor types of the human brain[5]. In this work we show the comparative results obtain in bolus track measurements performed in a high grade glioma rat model, using Gd- and Dy-containing compound as T2* contrast agents. Our main goal is to establish an optimal method to check the effectiveness of antiangiogenic therapies in high and low grade glioma murine models.

Methods

High grade gliomas were induced in Wistar rats (200-220 g) by stereotaxic injection of C6 cells in the right caudate nucleus. MRI evaluations were carried out between 21-25 days after the injection, in an horizontal 7T system (Bruker Pharmascan®) with a ^{1}H selective birdcage resonator of 38 mm. Animals were anesthetized with isofluorane 2% in oxygen, placed in a heated probe and physiologically monitored. Perfusion weighted imaging studies were performed using single-shot EPI acquisition and a solution of 0.3 M Gd-DTPA (Magnevist®) or 0.125 M Dy-DTPA (home made). The contrast agent was injected in the tail vein as a bolus (1 mL/kg bw) 10 seconds after starting acquisition. Both lanthanide complexes were assayed in the same animal, injecting Dy before because it has less appreciable effects on T1 than Gd, and waiting 3h until Gd injection. Acquisition parameters were the following: TR= 250 ms, TE = 7 ms, Av = 1, flip angle = 30^o, acquisition matrix = 64×80 corresponding to an in-plane resolution of 594x475 μm^2, number of repetitions = 150, total acquisition time = 38 seconds. Parametric perfusion maps (CBF, CBV and MTT) were generated on a pixel by pixel basis. Data were analyzed in a PC platform with a software application written in house (MatLab R2007a). In order to compute the perfusion maps, pixel time-evolution signals were obtained, and the values corresponding to the first seconds of each temporal series were considered to set the basal level. The following expression was fitted: $\Delta R_2^*(t) = -k.\ln(S(t)/S_0(t))$. Parametric maps were obtained for six slices (1.5 mm slice thickness) in each animal and four different regions (peripheral tumor, core tumor, white matter and cortex) in every case.

Results and Discussion

In the CBF, CBV and MTT maps obtained, we selected manually four brain regions containing at least 20 pixels each and yielding a value for every slice and every rat. Exactly the same pixels were analyzed both in Gd and Dy studies. Figure 1 summarizes the mean parametric data comparing measured either Gd-DTPA or Dy-DTPA. It can be noted that less quantity of paramagnetic metal leads more appreciable results using Dy- than Gd-complexe as contrast agent. Also, figure 1 shows higher absolute values in the parametric perfusion studies employing Dy, and a higher relative value when you compared regions to each other. On the other hand, in both DSC-MRI studies it can be appreciated lower CBF and CBV values in the core tumor than in other regions, similar values in peripheral tumor and white matter and the highest values in the brain cortex. MTT values are lower in the core tumor and similar in the other areas although in this case differences are more clearly estimated when Gd is employed.



a) CBF values employing either Gd or Dy-DTPA as T2* CA b) CBV values employing either Gd or Dy-DTPA as T2* CA c) MTT values employing either Gd or Dy-DTPA as T2* CA

Figure 1. Mean results obtained in DSC-MRI studies carried out in a high grade glioma rat model using two paramagnetic complexes as susceptibility contrast agent

Conclusions

Our results show that the use of Dy as paramagnetic susceptibility contrast agent in DSC MRI studies yields higher effects in perfusion parameters than the use of Gd. Dy complexes remain then as a better choice in perfusion MRI analysis in brain tumors because of their higher influence in T2 of the tissues. In the present glioma rat model that a this time point (21-25 days after injection of C6 cells) the core of the tumor is necrosed, so CBF and CBV are very low, and even peripheral tumor is not as well perfused as the brain cortex. The future steps in this study will be analyzing the results in the early stages of the tumor growth, when the tumor probably has an active neovascularization process and no necrosis appears yet.

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