Comparative Relaxivities and Efficacies of Gadolinium-based Commercial Contrast Agents.

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Introduction

Only a few papers were published comparing r1 relaxivities of commercial contrast media (CM) in human serum and plasma [1-4]. Rohrer et al. have reported data in favour of some agents. The relevant measurements were unfortunately not collected on dedicated relaxometric instruments but on 1.5 and 3T MR clinical systems. In the present study, we have investigated the relaxivities of nonspecific commercial CM by their NMRD profiles recorded on analytical systems from 0.1 to 300 MHz, and we have compared their respective efficacies in the main clinical application, brain tumors imaging.

Materials and Methods

Contrast agents: analyzed CM were Dotarem®(Gadoterate meglumine), Gadovist®(Gadobutrol), Prohance®(Gadoteridol), Magnevist®(Gadopentetate dimeglumine) and Omniscan®(Gadodiamide). For in vivo application, only the main two products, in terms of published safety and/or relaxivities, were injected; Dotarem® and Gadovist®.

NMRD profiles: data acquisition was performed on fast field cycling relaxometer (Stelar, Mede Italy), Minispec relaxometers and high resolution spectrometer (Bruker, Ettlingen, Germany) systems at 37°C. 120 MHz data were obtained by interpolation of the NMRD profiles. Contrast agent relaxivities were measured in water, serum, and on pooled human plasma to be the as close as possible to human applications. The contrast agent concentration was 1 mM.

In vivo evaluation: blinded and randomized iso-volume CM were injected at the dose of 0.1 mmolGd/kg body weight in C6 glioma rat (n=6 per CM). Standard spin echo sequence (TE/TR 10/500ms) was applied on a 2.35T system (Bruker, Ettlingen, Germany). Contrast-to-noise ratio (CNR) was followed before and during 30 minutes after injection. Data were blindly post-processed on GOA, a Matlab®-coded homemade software.

Relaxivities, simulated spin echo contrast and *in vivo* contrast-to-noise ratio were extracted and compared. For *in vivo* comparison, normality and variance's homogeneity of the residues were checked with Shapiro-Wilk's test and Bartlett's test. A Tukey (Bilateral) statistical analysis was performed. The relative error on the NMRD data is equal to 5%.

Results

r1 relaxivities at 1.5, 3 and 7T are presented in Table 1;

Table 1: r_1 in $mM^{-1}.s^{-1}$. 120MHz (3T) data were interpolated from NMRD profiles

Water	1,5T	3T*	7T	**Serum**	1,5T	3T*	7T	**H Plasma**	1,5T	3T*	7T
Magnevist	3.33	3.14	3.00	Magnevist	3.93	3.55	3.26	Magnevist	4.37	3.89	3.51
Omniscan	3.27	3.23	3.04	Omniscan	5.80	5.10	3.75	Omniscan	4.41	3.89	3.57
Dotarem	3.06	2.87	2.70	Dotarem	3.81	3.42	3.18	Dotarem	4.35	3.89	3.53
Prohance	3.07	2.89	2.75	Prohance	5.16	4.64	4.20	Prohance	4.07	3.76	3.49
Gadovist	3.08	2.92	2.80	Gadovist	5.15	4.64	4.19	Gadovist	4.86	4.34	3.81

In vitro, *in silico* and *in vivo* results at 2.35T are presented below:

Table 2: r1 ($mM^{-1}.s^{-1}$) at 1.5 T (dark red), 3T(red) and 7T (pink) in human plasma

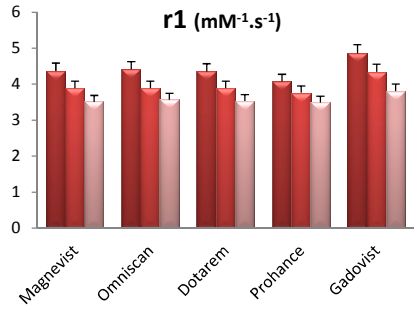


Fig 1: MR contrast-to-noise enhancement of Dotarem® and Gadovist® in C6 glioma.

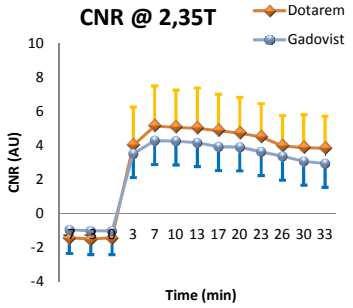


Fig 2: r_1 relaxivity ($mM^{-1}s^{-1}$), 10' post-injection *in silico* and *in vivo* MR signal (u.a) comparison.

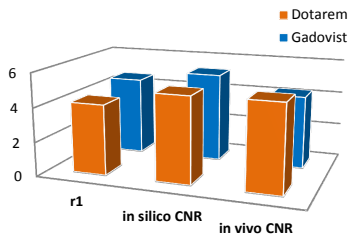
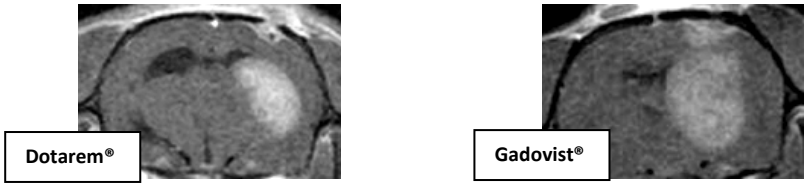


Fig3: Dotarem and Gadovist examples of enhancement tumors 10' after injection



Conclusion

r1 relaxivities are very closed between all the different Gd-Chelate (differences < 10%). No statistical *in vivo* contrast-to-noise difference was observed in the present study. This is in accordance to published data in human application where neither *in vivo* CNR nor diagnostic difference was observed between two marketed contrast agents [5]. In conclusion, r1 relaxivity is not really predictive of *in vivo* contrast agent efficacy, furthermore, in accordance with FDA and EMA recommendations, safety profiles of Gd-chelates are a major concern.

Lower r_1 relaxivities were extracted from the NMRD profiles as compared to published data obtained on non-dedicated MR systems (Tab1-2). No statistical differences were found on NMRD profiles in water, serum and pooled human plasma. r_1 relaxivities in human plasma for Dotarem® and Gadovist® are respectively 3.89±0.19 and 4.34±0.22 (Table2) at 3T. Due to nonlinear dependence between relaxivities and MR signal, smaller differences were observed in simulated spin echo CNR in SNC conditions (Fig2). Ten minutes after Gd injection, *in vivo* CNR are respectively 5.1 ± 2.2 and 4.3 ± 1.4 (Fig1-2). No statistical difference was observed (Dotarem®/Gadovist® p-Values is 0.77). This is illustrated by images shown in Fig3.

References : [1]Rohrer et al, Invest Radiol, 2005 [2]Noebauer-Huhmann et al. Invest. Radiol, 2010 [3] Pintaske et al. Invest Radiol, 2006 [4] Bleicher et al. AJNR 2008[4] Laurent et al. Contrast Media Mol Imaging, 2006 [5] Anzalone et al. Eur Radiol 2011