Determination of the Minimal Detectable Concentration of $MnCl_2$ by MRI

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INTRODUCTION

The divalent manganese cation (Mn^{2+}) behaves similarly to calcium, can be diffused through voltage-gated calcium channels in the brain, heart and pancreas [1]. In addition, the five unpaired electrons of this cation result in a high paramagnetic moment. Consequently, Mn^{2+} has been proposed as a unique tool to obtain magnetic resonance imaging (MRI) of neuronal function [2]. The recent production of PET nuclides of manganese [3, 4] offers the possibility of using this element for bimodal PET/MRI imaging that combines the high sensitivity of PET with the high resolution of MRI. However the different sensitivities of the modalities could be a problem, since to obtain a MRI is necessary to use millimolar concentrations (10^{-3} M) of the complex and just picomolar concentrations (10^{-12} M) are needed for a PET imaging.

In this work we assess the minimal amount of Mn^{2+} needed to obtain a MRI imaging with good contrast, to evaluate the possibility of performing bimodal PET/MRI.

MATERIALS AND METHODS

A solution 100 mM of $MnCl_2$ was prepared adding 0.9895 g of Manganese(II) chloride in 50 ml of water. Making dilution of this solution, 20 dilutions were prepared with different concentrations, ranging from 0.1 μM to 10 mM. The solutions, contained in 50 ml Falcon tubes, were placed inside a plastic box, which was filled with water (see Figure 1).

Fig. 1. Water phantom containing 20 tubes filled with $MnCl_2$ solutions.

To compare results obtained with $MnCl_2$ with those obtained with a contrast media (CM) currently used in the clinic, different solutions of Gadovist (gadobrutolo 1.0 mmol/ml solution), a gadolinium CM (used at a dose of 0.1 ml/kg), were also prepared, ranging from 0.005 mM to 20 mM.

MRI measurements were performed using a Siemens Healthcare PET/MR Biograph mMR (3 T of static magnetic field) with standard protocol for imaging of Gadolinium complexes, VIBE with T_1 weighing, TR=5.06 ms, and TE=2.26 ms.

RESULTS

The MR images obtained with $MnCl_2$ showed very low contrast for the solutions with low or high concentrations, as shown in Figure 2 (upper circles and bottom-left circles). The best contrast was found in the range from 75 μM to 2.5 mM. Concentrations under 10 μM did not produce any contrast. The range of concentration which allowed to obtain a good contrast with Gadovist was larger (from 0.1 mM to 20 mM) than the one of $MnCl_2$.

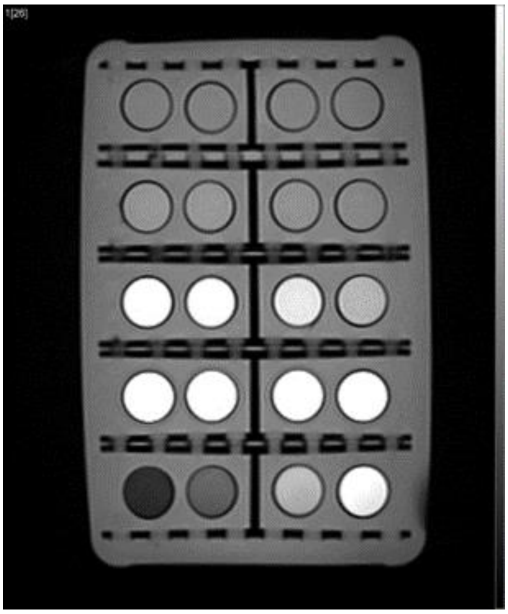
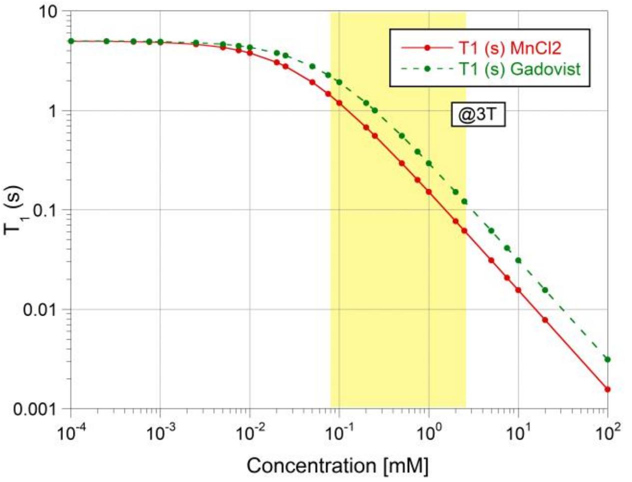
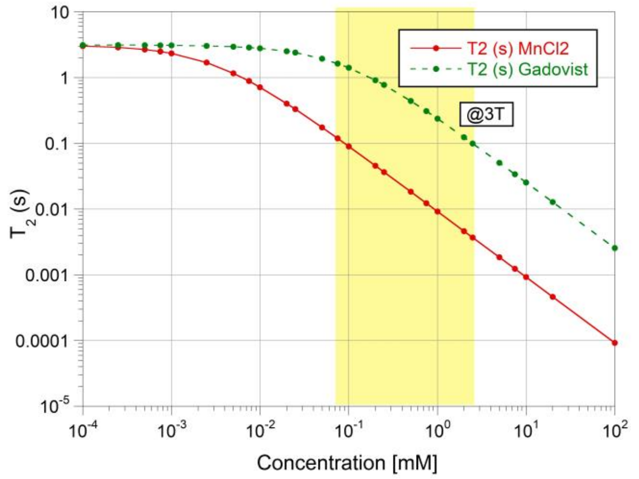


Fig. 2. MRI image of the water phantom containing 20 solutions of $MnCl_2$ at different concentrations (circles).



(a)



(b)

Fig. 3. The longitudinal, T_1, (a) and transverse, T_2, (b) relaxation times of $MnCl_2$- and Gadovist-aqueous solutions at different concentrations.

DISCUSSION

The longitudinal and transverse relaxation times of the investigated contrast media were assessed by assuming a linear relationship between relaxation rates ($1/T_i$, where i = 1, 2) and CM concentration [CM]:

$$\frac{1}{T_i} = \frac{1}{T_{i(0)}} + r_i \cdot [CM] \; ; \qquad (1)$$

where T_i denotes the longitudinal (T_1) or transverse (T_2) relaxation times of a solution containing the CM, $T_{i(0)}$ the relaxation times of the solvent (water in our measurements) without MRI-CM and r_1 and r_2 are the relaxivities of the CM.

The T_1- and T_2- relaxation times of the Mn and Gd solutions obtained using this relationship, the relaxation rates of water ($1/T_{1(0)}$= 0.21 s^{-1},$1/T_{2(0)}$=0.32 s^{-1}), the relaxivities of Gadovist in water at 3 T (r_1=3.2 $mM^{-1}s^{-1}$ and r_2=3.9 $mM^{-1}s^{-1}$) [5] and the relaxivities of $MnCl_2$ in water at 3 T (r_1=6.397 $mM^{-1}s^{-1}$ and r_2=108.266 $mM^{-1}s^{-1}$) [6] are plotted in Figure 3. Aqueous $MnCl_2$ has a large r_2/r_1 ratio (about 17) compared to Gd-based agent (r_2/r_1 about 1). The consequence is the presence of T_2-related signal decay at high CM concentrations, which is suboptimal for positive-contrast imaging and narrows the concentration range where enhancement can be obtained, evidenced by the yellow band in Figure 3 [7].

CONCLUSIONS

MRI measurements demonstrated that a good contrast can be obtained with $MnCl_2$ in a smaller range of concentrations when compared with Gadovist, but the minimum detectable concentration was quite similar (about 0.1 mM) with the two CM. However these results were obtained using an imaging protocol optimized for Gd contrast agents, having relaxation properties quite different from those of $MnCl_2$. To improve the detectability of $MnCl_2$ as a CM for MRI, imaging parameters must be optimized according to the expected concentration of the contrast agent in the human tissues of interest.

[1] J. Yang et al. *Front. Neurol.* 11 (2020) 16

[2] M.Brandt et al. *J.Label.Compd.Radiopharm.* 62 (2019) 541.

[3] S.A. Graves et al. *Sci Rep* 7 (2017).

[4] A.L Wooten et al. *PLoS One* 12 (2017**)** 3.

[5] M. Rohrer et al., Investigative Radiology 40 (2005) 715.

[6] K. Thangavel and E. Saritaş., Turk J Elec Eng & Comp Sci 25 (2017) 2108.

[7] J.T. Nofiele and H.M. Cheng, PLoS ONE 8(2013) e58617.