An Interaction of Gadodiamide with Cu^{+2} and Zn^{+2}

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Introduction

Gadolinium (Gd) based intravenous MRI contrast agents have recently been associated with nephrogenic systemic fibrosis (NSF) or nephrogenic fibrosing dermopathy (NFD).[1] Transmetallation between the Gd of the contrast agent and the endogenously available copper (Cu) or zinc (Zn) cations[2,3] is believed to play a role.[4] During this process, the Gd which is normally complexed to a ligand (L), is replaced by one or more cations (M^{+n}) as described by: $GdL + M^{+n} \leftrightarrow M_mL^{(mn-3)} + Gd^{+3}$. This reaction is of concern because it can deplete M^{+n} from the body while depositing Gd^{+3} in bone or liver.[4] Studies have shown an increased Cu and Zn excretion in urine after the use of certain contrast agents.[2,5] It is unclear if this increase is attributed to direct transmetallation with the Gd, complexation with other materials in the agent,[2,6] or a multi-step process in which Gd becomes bound to bone leaving a free ligand to complex with M^{+n}. We have studied the interaction of Cu^{+2} and Zn^{+2} with the contrast agent Gadodiamide (GdDTPA-BMA) by NMR relaxometry to determine *m*.

Methods

Aqueous solutions gadodiamide (Omniscan, GE Healthcare), $CuSO_4$, and $ZnSO_4$ were prepared using 18 MΩ·cm water. Proton NMR R_1 values were determined using a 300 MHz NMR spectrometer (Bruker DRX-300, Billerica, MA) with an inversion recovery pulse sequence. The relaxivities of gadodiamide, copper, and zinc solutions were determined respectively from solutions with $0 <$ [GdDTPA-BMA] < 0.9 mM, $0 <$ [Cu^{+2}] < 16 mM, and $0 <$ [Zn^{+2}] < 20 mM. Varying amounts of Cu^{+2} were added to a fixed concentration of 0.9 mM gadodiamide, and similarly Zn^{+2} to a fixed concentration of 1 mM gadodiamide. Plots of R_1 vs. [Cu^{+2}] or [Zn^{+2}] at these fixed gadodiamide concentrations were prepared as per the mole ratio method[7] to determine *m*.

Results & Discussion

The relaxivity of the aqueous gadodiamide, Cu^{+2}, and Zn^{+2} solutions were calculated from the slope of R_1 vs. concentration to be 4080, 670, and 0 $s^{-1}M^{-1}$ respectively. A plot of R_1 vs. [Cu^{+2}] (See Fig. 1.) showed a relaxivity of 3970 $s^{-1}M^{-1}$ for [Cu^{+2}] < 2.25 mM. At [Cu^{+2}] > 2.25 mM the relaxivity was 650 $s^{-1}M^{-1}$ or approximately equal to that for aqueous Cu^{+2}. These results support the formation of a complex in which two copper ions complex with the gadodiamide ligand DTPA-BMA. The inflection point is at 2.25 mM Cu^{+2} instead of the expected 1.8 mM because of the presence of caldiamide sodium in the Omniscan.[6] Assuming the formation of new material at [Cu^{+2}] < 2.25 mM, its relaxivity is 12030 $s^{-1}M^{-1}$. This new material can either be: 1.) a gadodiamide-2Cu^{+2} complex, or 2.) a mixture of Cu_2DTPA-BMA and Gd^{+3}. In both cases, the relaxivity is greater than that of Cu^{+2} and gadodiamide combined.

A plot of R_1 vs. [Zn^{+2}] showed a constant rise with a relaxivity of 160 $s^{-1}M^{-1}$. The absence of an inflection point in this plot indicates the absence of a complex under these conditions, even at Zn concentrations 20 times the gadodiamide. The increased relaxivity must be from the Gd and its small size indicates little transmetallation.

Conclusions

Two copper ions complex with the gadodiamide ligand DTPA-BMA. A similar complex is not seen between zinc and DTPA-BMA, despite the chemical similarities between Zn and Cu. These results warrant further investigation of the species present in mixtures of gadodiamide and Cu^{+2}.

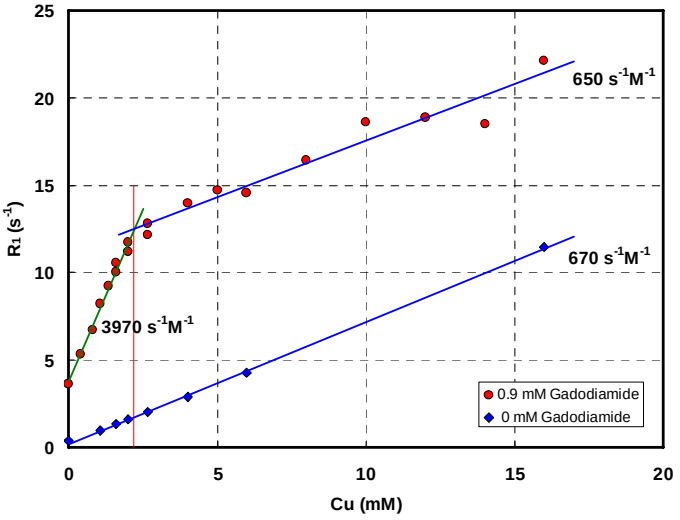

Figure 1. R_1 vs [Cu] at 300 MHz for aqueous solutions of copper (♦), and copper and 0.9 mM gadodiamide (●). The relaxivity of the copper with gadodiamide shows a break indicating that two copper ions complex with the gadodiamide ligand DTPA-BMA.

References

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