Evaluation of [Gd(TTDA-Py)] as a potential contrast agent in MR imaging of hepatobiliary system: An animal study

J-S. Hsu[1], G-C. Liu[1], T-S. Jaw[1], Y-M. Wang[2], S-H. Chen[3], K-B. Tsai[4], J-C. Jao[5]

[1]Medical Imaging, Kaohsiung Medical University, Kaohsiung, Taiwan, Taiwan, [2]Chemical Science, Kaohsiung Medical University, Kaohsiung, Taiwan, Taiwan, [3]Anima Research Center, Kaohsiung Medical University, Kaohsiung, Taiwan, Taiwan, [4]Pathology, Kaohsiung Medical University, Kaohsiung, Taiwan, Taiwan, [5]Faculty of Medical Radiation Technology, Kaohsiung Medical University, Kaohsiung, Taiwan, Taiwan

Synopsis

To evaluate the potential of a lipophilic paramagnetic complex, [Gd(TTDA-Py)] as liver MR contrast agent, we performed phantom experiments and MR imaging studie with normal and implanted hepatoma rats. The results revealed higher r1 relaxivity of [Gd(TTDA-Py)]than that of[Gd-DTPA]in human plasma and an intense enhancement of liver with a plateau during 5-30 minutes after intravenous injection of 0.1 mmol/kg [Gd(TTDA-Py)]. The efficacy of tumor characterization was similar t [Gd-DTPA]$^{2-}$ at the early dynamic phase. The liver-lesion signal difference –to-noise ratio (SDNR) were significantly improved with [Gd(TTDA-Py)]in the later phase when tumor enhancement has gradually washed out. The results indicated that [Gd(TTDA-Py)] has the potential of becoming a reliable liver MR contrast agent.

Introduction:

We have developed and characterized a new lipophilic paramagnetic complex, gadolium (III) 3,10-di(carboxymethyl)- 6-pyridylmethyl-3,6,10,-triazadodecanedioic acid [Gd(TTDA-Py)] [1] , designed for use as liver MR contrast agent [1]. The thermodynamic stability constant of this complex is similar to that of [Gd(DTPA)], and its R1 relaxivity is similar to [Gd(DTPA)]$^{2-}$ in aqueous solution [1]. To evaluate the potential of this contrast agent, the phantom experiments and MR imaging studies with norma rats and implanted hepatoma rats were performed.

Materials and Methods:

Phantom experiments were performed to evaluate r1 relaxivity and signal intensities on spin echo images for [Gd-DTPA] and [Gd(TTDA-Py)] in heparinized human plasm using a 3.0 T MR scaner with head coil. For MR imaging studies, 24 normal Wistar rats were separated into two groups: (1) Study group (n=12): intravenous injection of 0.1mmol/kg [Gd(TTDA-Py)], and (2) Control group (n=12) intravenous injection of 0.1mmol/kg[Gd(DTPA)]. Twenty-four rats with implanted HCC (CHA, Cheng hepatoma ascites, AS 30-D) were also separated into two groups as above. Sequential multislice, T1-weighted turbo field-echo (TFE) (TR/TE/Flip angle: 15 ms/6.1 ms/25^0 images were obtained before and after intravenous injection of contrast agents using a 1.5T MR scanner. To assess the kinetics of enhancement, the post-contrast scans were obtained every 14 seconds for 5 continuous scans and every 5 minutes for 30 minutes. MR images were analyzed to evaluate the time-enhancement change (enhancement % of signal-to-noise ratio, SNR) and liver-lesion signal difference –to-noise ratio (SDNR).

Results:

In human plasma, r1 relaxivity of [Gd(TTDA-Py)] (7.6 $mM^{-1}S^{-1)}$ is higher than that for [Gd(DTPA)] (4.62 $mM^{-1}S^{-1}$)(r^2 = 0.99). The maximal enhancement of [Gd(TTDA-Py)]and [Gd(DTPA)]five minutes after injection were 160±29% vs 50 ±8% in liver (p<0.001), 568±91% vs 484±87 % in cardiac chambers (p< 0.05), 164±30% vs 115±26% in renal cortex (p< 0.01), and 167±31% vs 165±33% in renal medulla (p> 0.05), respectively. In addition, the enhancement% of liver persisted up to 30 minute observation period. Enhancement% of the CHA tumors and the cardiac chambers were larger for[Gd(TTDA-Py)]while renal excretion was shown for all rats five minutes after injection of[Gd(TTDA-Py)]and[Gd(DTPA)]. The liver-lesion SDNRs were significantly better with injection of [Gd(TTDA-Py)] than those with injection of[Gd(DTPA)]after 5 minutes post-contrast. (P<0.05)

Discussion:

Phantom study demonstated a large T1 shorting effect of [Gd(TTDA-Py)]in human plasma than that of [Gd(DTPA)], a difference which is though to be related to the bindin of [Gd(TTDA-Py)]to plasma proteins. MR study demonstrated a prolonged intense enhancement of liver after injection of 0.1 mmol/kg [Gd(TTDA-PY)]. The lipophilic character of [Gd(TTDA-Py)] and its higher r1 relaxicity in plasma and vascular retention might contribute to this. With this contrast agent, the dynamic changes of tumo enhancement can be appreciated in the early phase of contrast study, and the liver-lesion discrimination will be significantly improved at the phase of liver enhancement i.e 5 – 30 minutes after injection of [Gd(TTDA-Py)]. Therefore, it will be very helful in both charactization and detection of liver lesions.

Conclusion:

Our preliminary results indicated that[Gd(TTDA-Py)]has the potential of becoming a reliable magnetopharmacetical of liver MR contrast agent.

Reference:

1. Cheng TH, Wang YM. Polyhedron 19: 2027-2037, 2000.

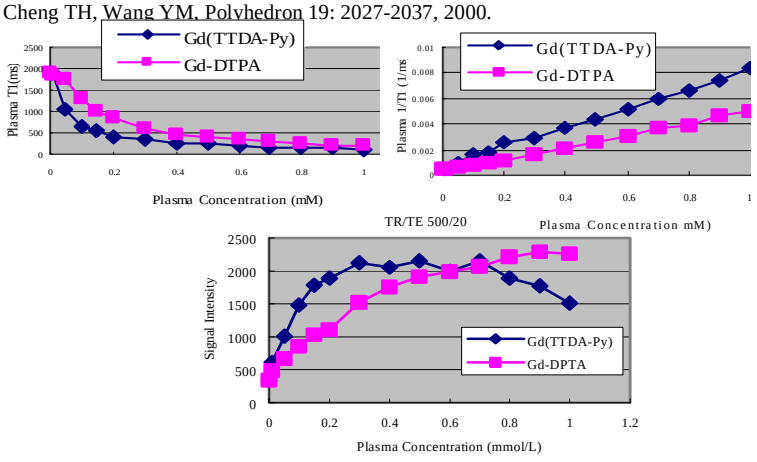

Fig 1. T1 relaxation times (A), 1/T1 (B) and signal intensities on TFE images (C) of phantoms containing [Gd(TTDA-Py)] and [Gd(DTPA)]. Changes in relaxation parameters are much greater with [Gd(TTDA-Py)] owing to higher relaxivity. Signal intensities are much greater for [Gd(TTDA-Py)] at lower concentration owing to higher relaxivity.

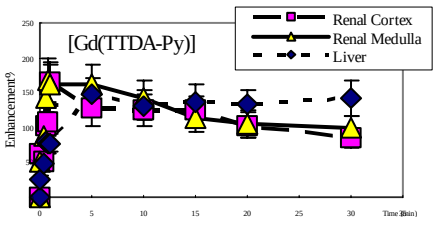

Fig.2. Time-enhancement change of the normal rats after injection of 0.1 mmol/kg [Gd(TTDA-PY)] with T1-weighted TFE sequence (TR/TE/flip angle 15ms/6ms/25^0). The enhancement of liver and kindey were persistent up to 30 minutes after intravenous administration of [Gd(TTDA-Py)]. (mean ± standard deviation, n=12 in each group)

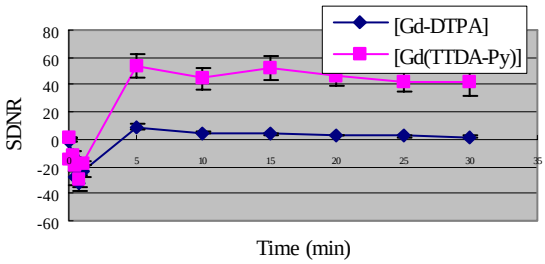

Fig.3. The liver-lesion SDNR in rats with hepatoma after injection of [Gd(TTDA-PY)] and [Gd-DTPA]. (mean± standard deviation, n=12 in each group)

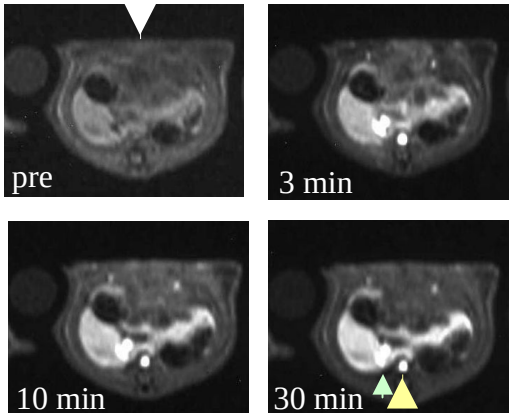

Fig.4. Sequential T1-weighted TFE images of a rat with implanted CHA tumor (arrowhead) before and after intravenous injection of Gd(TTDA-Py). There is persistent enhancement of liver, aorta (thick arrow) and inferior vena cava (thin arrow) at 30 minutes after injection of Gd(TTDA-Py).