The Liver Enhancement Patterns of a New Dual Contrast MR Agents with moderate molecular weight

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Introduction

Hepatobiliary MR agents have been proven to improve lesion detectability and diagnostic accuracy. In addition, the dual contrast agent has been sought because its ability to shorten both T1 and T2 relaxation times with single injection. In this study, we synthesize a new hepatobiliary dual contrast MR agent and evaluate the liver enhancement patterns using animal tumor model.

Material and Methods

CM synthesis: A mixture of 1,2-Di-(2-ethylacid)-4,5-dicyanobenzene (2.01g) and manganese chloride (0.37g) was heated at 310 C for 36 hours. The mixture was then purified by silica gel column chromatography (CHCl3 : CH3OH = 98:2 volume ratio) to obtain 1.04 g of manganese phthalocyanine (MnPC) with 2000 daltons molecular weight.

Tumor model: The VX-2 carcinoma was experimentally induced in adult New Zealand white rabbits (3.1 – 5.5 kg: mean 4.2 kg). The tumors were made in both right and central lobe of the rabbit liver by injection of 0.3 to 0.5 ml suspension of tumor cell suspension with an 18 gauge biopsy needle. A hemostat was used to prevent bleeding and leakage of tumor cell suspension into the peritoneal cavity after removal of the needle from the puncture sites.

MR Relaxometry and Imaging: Both MR relaxometry and imaging studies were performed on a 1.5T scanner (Vision Plus, Siemens, Erlangen, Germany). The standard human extremity coil was employed. For relaxivity measurements, T1 and T2 of aqueous solutions were measured by inversion recovery and CPMG technique respectively. The pre- and post-contrast T1- and T2-weighted images were obtained before and after bolus injection of MnPC (0.1 mmol/kg) and MnDPDP (0.01 mmol/kg) via ear vein. Both FLASH (TR/TE = 11/4.2 msec, flip angle 15°) and Spin-echo (TR/TE = 418/12 msec) sequences were employed for T1WI and Fast spin-echo . (TR/TE = 1500/90 msec, ETL=8) for T2WI. Each agent was injected with at least 24 hours time interval to make sure clearance of the agent from the body. The sequential MR images were obtained up to 50 minutes after contrast injection. The liver enhancement patterns of a new dual contrast agent (MnPC) and MnDPDP were evaluated to estimate the characteristic features of each agents.

Results

Longitudinal (R1) and transverse (R2) relaxivities of MnPC in aqueous solution were (7.28±0.14) $sec^{-1}mM^{-1}$ and (55.56±2.85) $sec^{-1}mM^{-1}$ respectively. The R2 value of MnPC was significantly higher than the value of MnDPDP whereas the R1 value was similar to MnDPDP at 64 MHz. The pre- and post-contrast T1WI's of normal rabbit are shown in Fig. 1. After injection of MnPC, the liver parenchyma was significantly enhanced. A filling of contrast agent in gall bladder, which was shown on the delayed image, suggests that MnPC is an hepatobiliary agent. In addition, the enhancement of kidney with MnPC reflects the agent has dual excretion pathway. For a tumor induced rabbit, MnPC enhances both the normal portion of liver parenchyma and the tumor rim (Fig. 2). Therefore, each small tumor segments are well differentiated. On the other hand, MnDPDP does not enhance the tumor rim and thus the tumor segments are not well differentiated. The post-contrast T2WI of tumor induced liver of a rabbit with MnPC, which shows a signal decrease of normal parenchyma, suggests strong T2 effect of this agent (Fig. 3). Therefore, MnPC reveals dual contrast (T1 and T2) enhancement characteristics.

Discussion

Currently, two classes of the liver-specific MR agents are proposed. One class is hepatobiliary agent and the other is RES agent. The hepatobiliary MR agents, which are uptaken by hepatocyte, are mostly paramagnetic chelates with small molecular-weight and shows T1 effect. On the other hand, the RES agents, which rapidly undergo phagocytosis by hepatic Kupffer cells, are superparamagnetic iron oxides with large molecular-weight and used as T2 agent. In this study, a newly synthesized MnPC with moderate molecular weight shows both T1 and T2 effects and thus has a potential for a dual contrast agent. Another interesting finding is that the enhancement characteristic of MnPC is much different from that of MnDPDP on T1-weighted images. Although the detailed mechanism of hepatocyte uptake of MnPC remained to be understood, the strong peri-tumoral rim enhancement with MnPC seems to have a clinical advantage. Beside of enhancing lesion conspicuity, the rim enhancement might be an index of tumor angiogenesis such as a permeability change of vascular wall.