The Comparative Imaging Study on Mn-phthalocyanine and Mangafodipir trisodium in Experimental VX2 Animal Model

Hyun-Jeong Park[1], Sung-Min Ko[2], Yongmin Chang[3], Yong-Sun Kim[3]

Purpose : To measure the NMR relaxation properties of MnPC, to observe the characteristics of liver enhancement patterns on MR images in experimentally implanted rabbit VX2 tumor model, and to estimate the possibility of tissue specific contrast agent for MnPC in comparison with the hepatobiliary agent.

Materials and Methods : Phthalocyanine (PC) was chelated with paramagnetic ions, manganese (Mn). 2.01 g (5.2 mmol) of phthalocyanine was mixed with 0.37 g (1.4 mmol) of Mn chloride at 310℃ for 36 hours and then purified by chromatography ($CHCl_3$: CH_3OH = 98:2, volume ratio) to obtain 1.04 g (46%) of MnPC (molecular weight = 2000 daltons). The T1/T2 relaxivity (R1/R2) for MnPC were determined at a 1.5 T (64 MHz) MR spectrometer. VX2 tumor model was experimentally implanted in the liver parenchyma of rabbits. All MR studies were performed on 1.5 T. The human extremity radio frequency coil of a bird cage type was employed. MR images were acquired at 17 to 24 days after VX2 carcinoma implantation. 4 mmol/kg MnPC and 0.01 mmol/kg Mn-DPDP were injected via the ear vein of rabbits. T1-weighted images were obtained with spin-echo (TR/TE = 516/14 msec) and fast multiplanar spoiled gradient recalled (TR/TE = 80/4 msec, 60° flip angle) pulse sequence. Fast spin-echo (TR/TE = 1200/85 msec) was used to obtain the T2-weighted images.

Results : The value of T1/T2 relaxivity (R1/R2) of MnPC was 7.28 $mM^{-1}S^{-1}$ and 55.56 $mM^{-1}S^{-1}$ respectively at 1.5 T (64 MHz). Because the T2 relaxivity of MnPC that bonded strongly, covalently manganese with phthalocyanine was very high, the signal intensity of liver parenchyma was decreased on postcontrast T2-weighted images and we could easily distinguish the VX2 carcinoma within the liver parenchyma. When MnPC was administrated intravenously, the tumor margin delineation was more remarkable than Mn-DPDP-enhanced images. The enhancement of liver parenchyma with MnPC persisted at relatively high levels over at least one hour after injection of the contrast agents.

Conclusion : The hepatic uptake and biliary excretion of MnPC, which are similar to Mn-DPDP, suggest that this agent is a new liver-specific agent. Also, MnPC seems to

JKSMRM 8:32-41(2004)

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Received; December 10, 2003, acceepted; May 7, 2004

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be used as a dual contrast agent (T1 and T2) with high T2 relaxivity. However, it is warranted that MnPC needs further investigation as a potential contrast agent for MR imaging of the liver. That is, further characterizations of MnPC are needed in vivo and in vitro before clinical trials. The diagnostic potential of MnPC will also have to be examined more in the animal models of additional types.

Index words : Contrast agent
Liver
VX2 tumor
Macromolecular
Rabbit

Introduction

The liver contrast media(CM) for MRI are divided into the following four groups by their biodistribution and contrast effects: extracellular, reticuloendothelial, hepatobiliary and blood pool(macromolecular) agents (1-3). Because extracellular fluid contrast media such as Gd-DTPA, Gd-DOTA, and Gd-DTPA-BMA exhibit no tissue specificity and rapid distribution from the vascular compartment to the extracellular interstitial space, their use requires both rapid injection and dynamic imaging. The rapid distribution of these agents also limits the accurate lesion detection (1, 4). The Gd chelates conjugated to macromolecular backbones or polymeric ones have been developed, including such as albumin-(Gd-DTPA) (5, 6), dextran-(Gd-DTPA) (7), and polylysin-(Gd-DTPA) (8, 9). Macromolecular contrast media(MMCM) have several advantages over small molecualr contrast media (SMCM). First, the long intravascular residence time of MMCM does not limit the data collection time. Because these MMCM have higher relaxivity values than existing SMCM, the enhancement effects of images obtained after a single bolus injection will be similar to the enhancement effects of the existing SMCM (2, 10). Another advantage of MMCM is the possibility as tissue-specific contrast agent. Up to now, the developmental strategies for tissue-specific contrast agents made up of bonding the lipophilic materials to SMCM. These compounds elevate the lipophilicity of contrast agents, consequently, they made higher lipophilicity for the phospholipid bilayer that formed the cell membrane. The lipophilic Gd-chelate contrast agents include Gd-EOB-DTPA, Gd-BOPTA, and etc (11-13). We developed new macromolecular MR contrast agent, manganese phthalocyanine (MnPC), with molecular weights of approximately 2000 daltons. The purpose of this study is to measure the NMR relaxation properties of MnPC and to observe the characteristics of liver enhancement patterns on MR images in experimentally implanted rabbit VX2 tumor model. We also attempted to estimate the possibility of tissue-specific contrast agent for MnPC in comparison with the hepatobiliary agent.

Materials and Methods

Tumor Implantation

The experiments were carried out in 16 adult New Zealand white rabbits weighing between 1.5 and 3.5 kg. The VX2 tumor was obtained from Seoul National University Hospital, and grown for 3 weeks on the hind legs of each donor rabbits. The VX2 tumor was maintained through serial transplantation into the hind limb muscle of rabbits. The donor rabbit was killed by intravenous injection of 90 mg/kg thiopental sodium. The VX2 tumor was aseptically stripped from the surrounding connective tissues. Fragments of tissue taken from the tumor in donor rabbits were then diced into approximately $1 \times 1 \times 1$ mm with scissors and homogenized in PBS (13).

All recipient rabbits were anesthetized with an intramuscular injection of 5 mg/kg xylazine hydrochloride and 35 ml ketamine hydrochloride. After midline incision, the central and right lobe of liver were exposed. Each of the recipient rabbits was injected with 0.5 ml VX2 carcinoma cell suspension into these lobes. The injection of tumor cell suspension was carried with use of a 18-gauge needle. The tumor suspension was injected s-

lowly into the liver parenchyma, and then the needle was removed. 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 site (14).

The synthesis and administration of Mn-phthalocyanine

Phthalocyanine was chelated with paramagnetic ion, Mn. A mixture of PC (2.01 g, 5.2 mmol) and manganese chloride (0.37 g, 1.4 mmol) was heated at 310°... for 36 hours. The mixture was purified by silica gel column chromatography ($CHCl_3$: CH_3OH = 98:2, volume ratio) to obtain 1.04 g (46%) of MnPC with 2000 daltons molecular weight. Mn-PC was diluted into 20 mmol concentration with 0.8% sterile normal saline. For our studies, 0.2 ml/kg MnPC was rapidly administered into the ear vein of rabbits.

Mn-DPDP

Mangafodipir trisodium (TELASCAN®, Nycomed, Oslo, Norway) is a paramagnetic, hepatobiliary-specific T1 agent. Manganese is chelated with DPDP, which is the catalytically active form of vitamin B_6. This agent is taken up by hepatocytes and excreted into the bile and urine (15-17). After baseline MRI scan, 0.01 mmol/kg of Mn-DPDP was slowly administered over the period of 5-10 minutes into the ear vein of rabbits.

Proton Relaxivity

MnPC was diluted into 0.1 mmol concentration with 0.8% sterile normal saline. The T1/T2 relaxivity(R1/R2) for MnPC was determined at a 1.5 T (64 MHz) MR spectrometer (Simens Vision Plus). The saturation recovery technique using 90-180° inversion RF pulse was employed to measure spin-lattice relaxation time. On the other hand, spin-spin relaxation time was determined with Carr-Purcell-Meiboon- Gill (CPMG) pulse.

In vivo Magnetic Resonance Imaging

All MR studies were performed on 1.5 T scanner (GE Signa Advantage, GE Medical System, U.S.A.). The human extremity radio frequency coil of a bird cage type was employed. MR images were acquired at 17 to 24 days after implantation. The animals were anesthetized via intramuscular injection of a mixture of 5 mg/kg xylazine hydrochloride and 35 mg/kg ketamine hydrochloride.

Three sequences were used, and each images were obtained before and after CM administration. T1WI were obtained with spin-echo (SE) and Fast Multiplanar Spoiled Gradient Recalled (FMPSPGR) pulse sequence. The parameters for T1-weighted SE imaging were as follows: TR of 516 msec, TE of 14 msec, FOV 12 cm, ma-

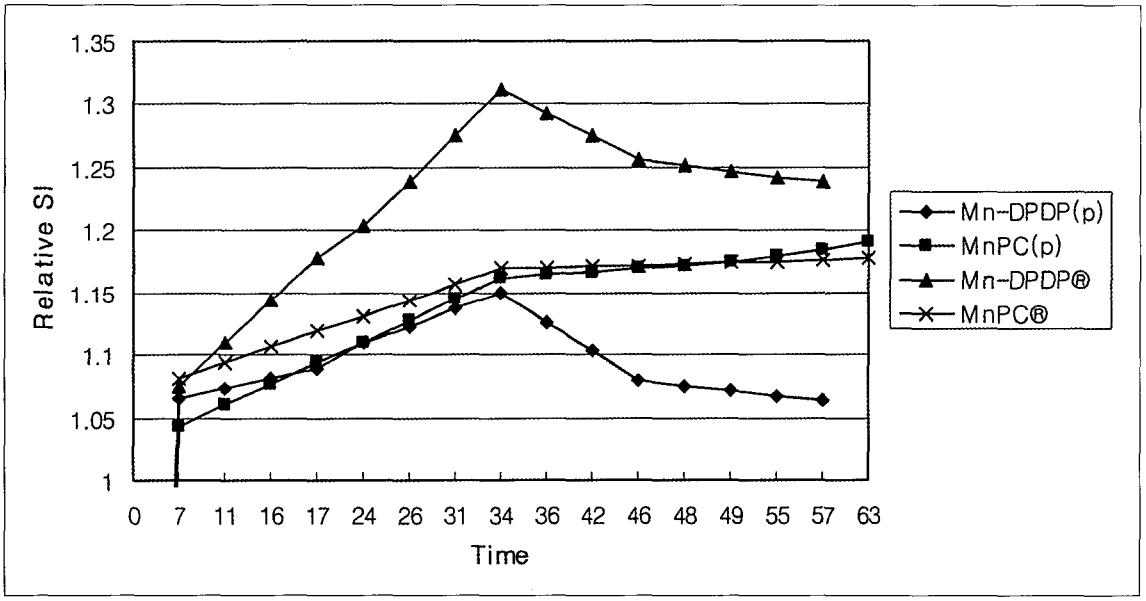

Fig. 1. ROI plots of relative SI of the normal liver parenchyma (Ⓟ) and the VX2 carcinoma rim (®) from the T1-weighted SE images for MnPC and Mn-DPDP. SI of the liver parenchyma and the tumor rim was gradually increased and maintained continuously.

trix 128 × 256, 2 NEX, and slice thickness of 3 mm (gap 1 mm). The parameters for the dynamic T1-weighted FMPSPGR imaging were as follows: 80 msec/4 msec (TR/TE), flip angle 60 degrees, FOV 12 cm, bandwidth 16 KHz, matrix 128 × 256, 2 NEX, and slice thickness of 3 mm (gap 1 mm). The parameters for T2-weighted fast spin-echo (FSE) imaging were as follows: 1200 msec/85 msec (TR/TE), FOV 12 cm, matrix 128 × 256, 2 NEX, and slice thickness of 3 mm (gap 1 mm). Both pre- and postenhanced MR images were used identical pulse sequence parameters.

Data Analysis

SI values for the liver parenchyma and the VX2 carcinoma were obtained for subsequent, quantitative analysis. ROI measurements were made as a function of time after intravenous injection of contrast agents in the normal liver parenchyma and the VX2 tumor rim. SI versus time curves from each ROI were individually normalized to the unenhanced baseline value, and then averaged over all regions on all slices for each tissue type.

Results

Proton Relaxivity

The value of T1/T2 relaxivity (R1/R2) of MnPC was 7.28 $mM^{-1}S^{-1}$ for T1 and 55.56 $mM^{-1}S^{-1}$ for T2 respectively at 1.5 T (64 MHz).

In vivo Magnetic Resonance Images

a. Mn-phthalocyanine

The liver parenchyma and the VX2 tumor lesions

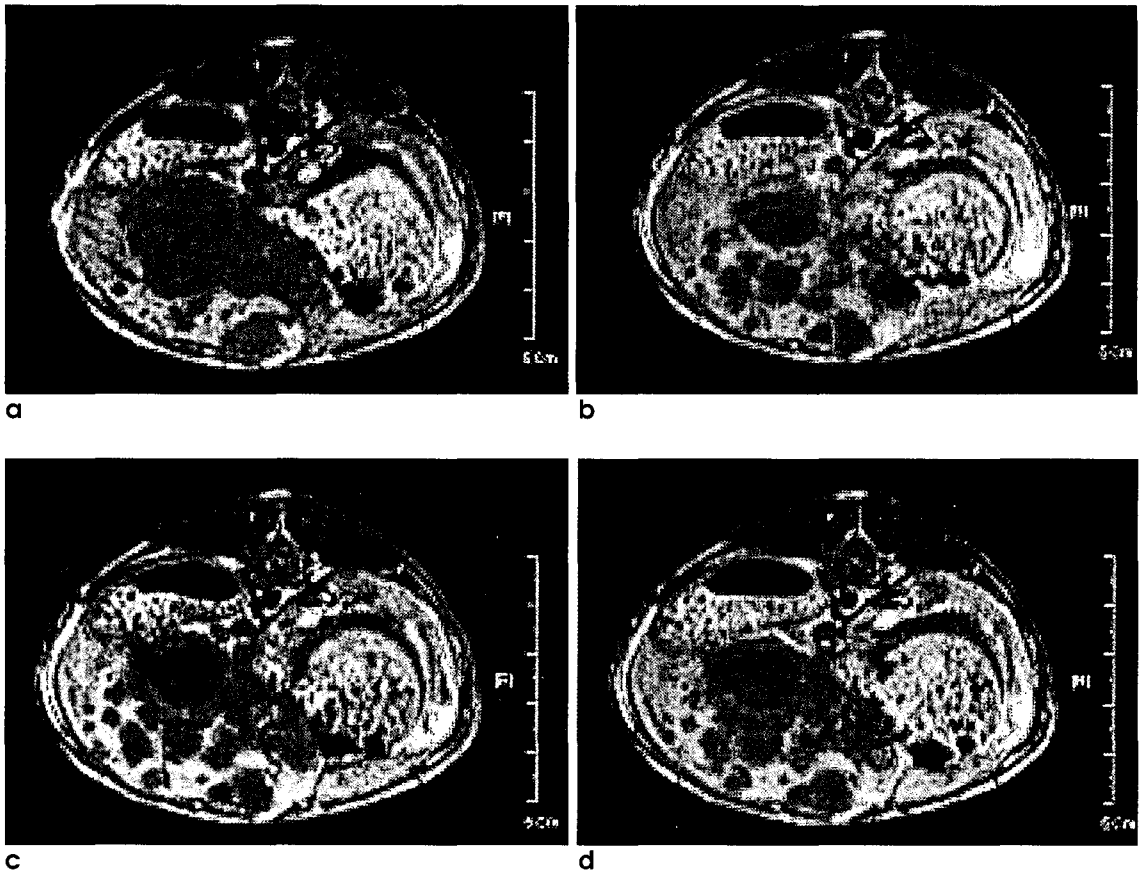

Fig. 2. Spin-echo images(TR/TE = 516/14 msec) of MnPC in rabbit liver with experimentally implanted VX2 tumors. **a.** Before contrast agent. **b.** 12 minutes after intravenous injection of 4 mmol/ß∏ MnPC. SI of the liver parenchyma and the tumor rim began to be increased. **c.** 34 minutes after injection. Tumor areas and surrounding connective tissue areas could be clearly separated due to significantly increased SI of the rim. **d.** 63 minutes after injection. SI of the liver parenchyma and tumor rim was gradually increased all during examination. No contrast enhancement was observed in the central zone that were necrotic areas.

showed homogeneous patterns on precontrast T1WI (Fig. 2a, 3a) and heterogeneous patterns on unenhanced T2WI (Fig. 4a). The VX2 tumor was hypointense on T1WI (Fig. 2a, 3a) and hyperintense on T2WI (Fig. 4a), compared with the normal liver parenchyma. On T1WI, the liver parenchyma was strongly enhanced after intravenous injection of MnPC. SI of the liver parenchyma was gradually increased, and the increase in the tumor-to-normal liver contrast was maintained continuously (Fig. 1). Prominent rings surrounded the tumor masses with a darker core. Tumor areas and surrounding connective tissue areas could be clearly separated on postcontrast T1-weighted SE images due to significantly increased SI of the tumor rim (Fig. 2b-d). The tumor was easily distinguishable from the necrotic or cystic inner core also on the postcontrast T1-weighted FMPSPGR images. Enhancement of the central viable tumors from about 30 minutes after injection of MnPC was not as sharp as postcontrast T1-weighted SE images, but the increase in the tumor-to-normal liver contrast was continuously maintained to some extent all during examination (Fig. 3b-d). It was noteworthy that SI of the liver parenchyma was decreased on enhanced T2-weighted FSE. This phenomenon made possible the clear discrimination between the liver parenchyma and the viable tumor regions, which could not be observed after intravenous injection of T1 contrast agents (Fig. 4b-d). On both T1- and T2-weighted images, no contrast enhancement was observed in the central zone that were necrotic areas histopathologically, and fibrotic portions that were obscurely observed on precontrast T1WI were seen clearly.

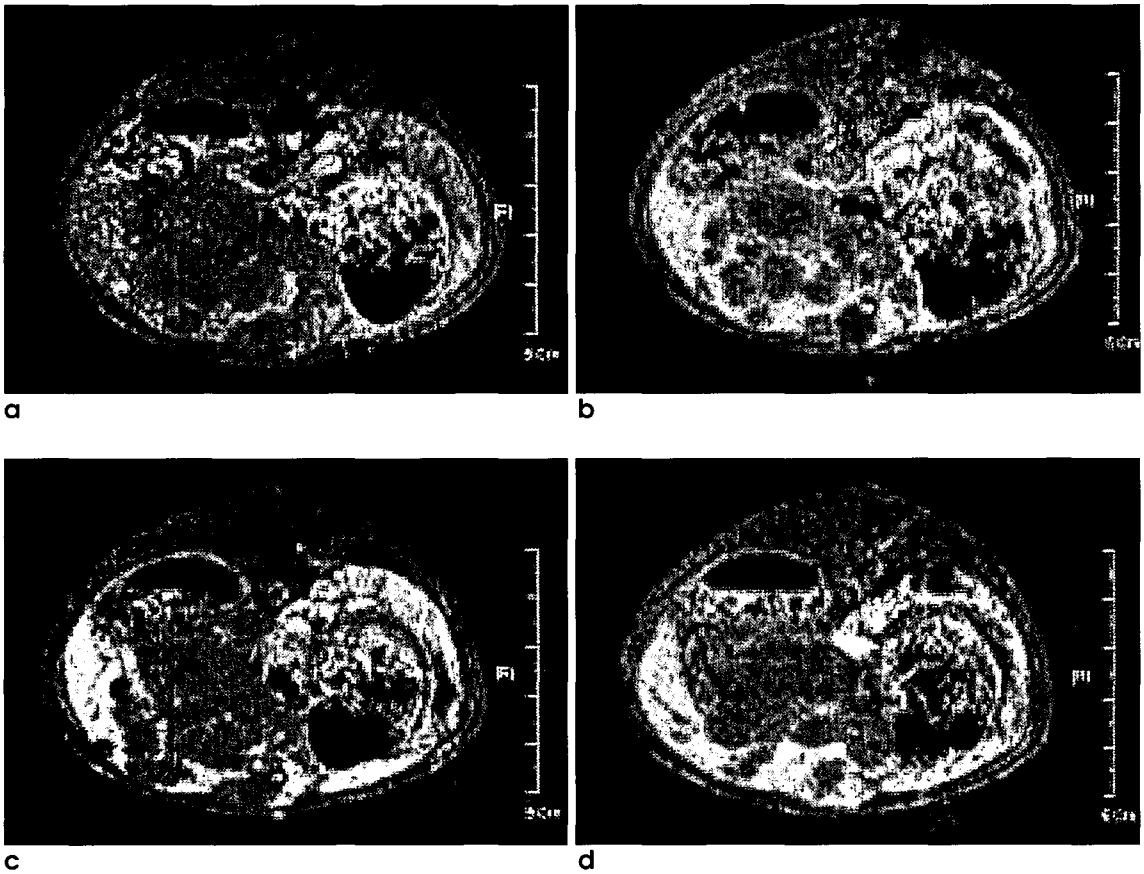

Fig. 3. FMPSPGR images(TR/TE = 516/14 msec) of MnPC in rabbit liver with experimentally implanted VX2 tumors. **a.** Before contrast agent. **b.** 8 minutes after intravenous injection of 4 mmol/ßÎ MnPC. Tumor periphery was enhanced strongly in a rim pattern, while central viable tumor showed an intermediate enhancement. The tumor was easily distinguishable from the necrotic or cystic inner core. **c.** 29 minutes after injection. There was no contrast enhancement at the center of the necrotic regions. **d.** 59 minutes after injection. The increase in the tumor-to-normal liver contrast was continuously maintained to some extent.

b. Mn-DPDP

The liver parenchyma and the VX2 tumor showed homogenous SI on precontrast T1WI (Fig. 5a, 6a). The SI of tumor lesion was lower than the normal liver parenchyma on all pre- and postcontrast T1WI. The liver parenchyma is strongly enhanced after injection of this tissue-specific agent. The increased signal enhancement of the liver parenchyma thus improved the visualization of the VX2 tumor lesion on postcontrast T1WI relative to the precontrast images. Enhancement of the liver parenchyma was relatively well maintained during examination. A tumor rim, which is hyperintense, is well defined on postcontrast images. No uptake of the contrast agent into the necrotic area was seen after intravenous administration of Mn-DPDP(Fig. 5b-d, 6b-d). The maximum liver-to-tumor contrast was reached in about 35 minutes after intravenous infusion of Mn-DPDP (Fig. 1). Unenhanced T2-weighted FSE showed hyperintense tumor rim and hypointense fibrotic that were obscurely observed on precontrast T1WI (Fig. 6b).

Discussion

Our laboratory recently developed the relatively macromolecular MR contrast agent, Mn-phthalocyanine, that had the molecular weights of 2000 daltons. The effect of MnPC on water proton relaxation was determined *in vitro*. In case of MnPC, an increased efficiency in proton relaxation enhancement was observed when paramagnetic ions were complexed to macromolecular ligand. The R1 measured with 0.1 mmol MnPC was 7.28 $mM^{-1}S^{-1}$ at 1.5 T (64 MHz), and consequently

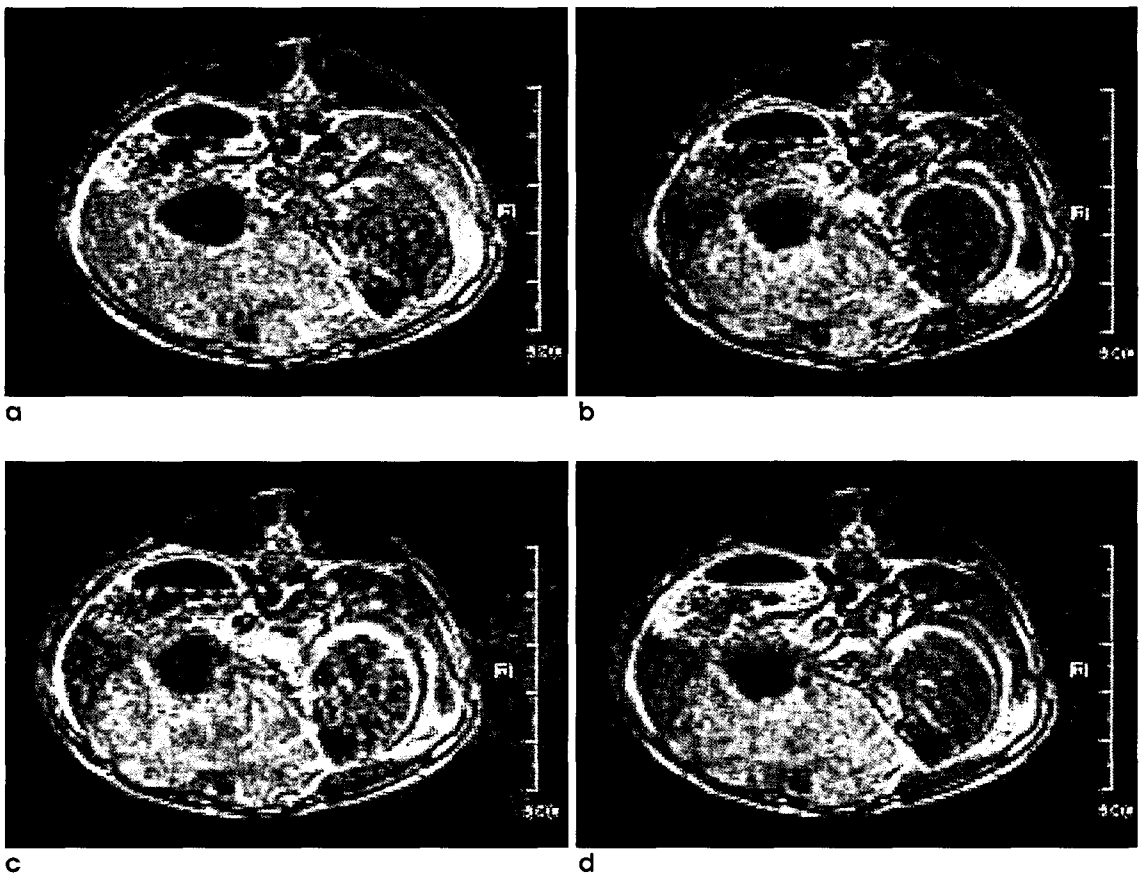

Fig. 4. FSE images (TR/TE = 1200/85 msec) of MnPC in rabbit liver with experimentally implanted VX2 tumors. **a.** Before contrast agent. **b.** 9 minutes after intravenous injection of 4 mmol/kg MnPC. SI of the liver parenchyma began to be decreased. Compartmentalized necrotic regions were seen. **c.** 30 minutes after injection. Decreased SI in the liver parenchyma made possible the differentiation between the liver parenchyma and the viable tumor lesions, which could not be observed after intravenous injection of T1 contrast agents. **d.** 60 minutes after injection. The increase in the tumor-to-normal liver contrast was relatively well maintained.

attributed to a slowing of tumbling rate of MnPC. In addition, the value of R2 of MnPC was 55.56 $mM^{-1}S^{-1}$. It was noteworthy that the R2 value of MnPC was much higher than the commonly used MR contrast agents (18). We expected that MnPC would be able to be used as T2 agent as well as T1 agent, adjusting imaging parameters properly on T2WI. This possibility was well demonstrated in the experimentally implanted VX2 tumor model of rabbits.

T1 contrast agent such as Mn-DPDP could show no significant discrimination between the liver parenchyma and the viable tumor on enhanced T2WI (16, 17, 19, 20). In this study, high T2 relaxivity of MnPC, resulting from strongly, covalently bonded manganese with phthaocyanine, suggests that MnPC will be used as T2 agent as well as T1 agent. As a result, we determined the SI of the liver parenchyma was decreased on postcontrast T2-weighted FSE after intravenous injection of MnPC, and we could easily distinguish the VX2 carcinoma within the liver parenchyma (Fig. 4).

When MnPC was administrated intravenously, the tumor margin delineation was more remarkable than the MR images enhanced with Mn-DPDP (Fig. 2-4) (19, 20). On all enhanced T1WI, strongly enhanced areas corresponded to richly vascularized connective tissues and viable tumor tissues, whereas nonenhanced areas corresponded to nonvascularized necrotic tissue histologically. No contrast enhancement was observed in the central zone that were necrotic areas histologically (21-23). In the current study, the change in the SI of liver parenchyma after intravenous injection of CM was measured. The enhancement of normal liver parenchyma

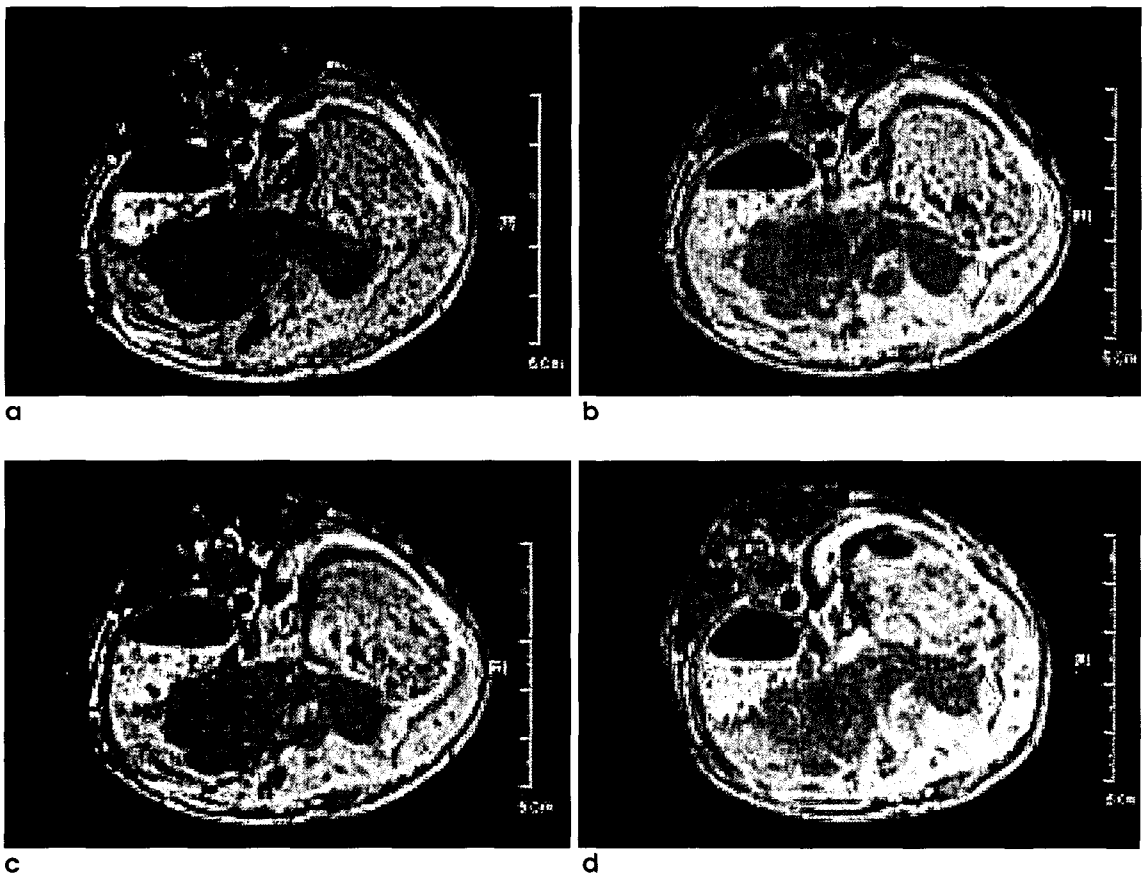

Fig. 5. Spin-echo images (TR/TE = 516/14 msec) of Mn-DPDP in rabbit liver with experimentally implanted VX2 tumors. **a.** Before contrast agent. **b.** 12 minutes after intravenous injection of 0.01 mmol/kg Mn-DPDP. The liver parenchyma was strongly enhanced, but the central viable tumor was not enhanced very much. **c.** 34 minutes after injection. SI of the liver parenchyma and the tumor rim showed the maximum value. **d.** 63 minutes after injection. Enhancement of the liver parenchyma was relatively well maintained. No contrast enhancement was observed in the necrotic areas.

with MnPC persisted at relatively high levels over at least one hour after injection of CM (Fig. 1). The gradual, persistent, high enhancement patterns of VX2 carcinoma with MnPC are thought to reflect the leakiness of the macromolecules into the interstitial space due to high vascular permeability.

The hepatobiliary contrast agents were taken up into the hepatocytes, and then excreted into bile and urine (1-3). In case of Mn-DPDP, it is dissociated to free manganese and DPDP after undergoing rapid dephosphorylation by alkaline phosphatase. Because DPDP is chemically similar to vitamin B6, this agent is taken up into the hepatocytes via the cell membrane transport system (1, 15-17). The previous study showed that the signal enhancement of the kidney and the gallbladder occurred after intravenous injection of MnPC on the MR images (18). The mechanisms by which the hepatocytes extract MnPC from the blood and secrete them into bile were not refined in this study. Therefore, preclinical examination should be performed to determine how MnPC is taken up by the hepatocytes.

Compared with the current developmental directions of MMCM, MnPC is analogous with MS-325 in that the paramagnetic materials are strongly combined with the large molecular ligands (24, 25). Therefore, it is a new class of the MMCM that has a similar property with S-PIO in that they exhibit high T2 effect (2, 10). This agent is T1 and T2 contrast agent but show no blood pool effect like other MMCM.

MnPC is a relatively new contrast agent for MR imaging, but its pharmacokinetic or pharmacodynamic properties are not yet fully determined. The hepatic uptake and biliary excretion of MnPC, which are similar to Mn-DPDP, suggest that this agent is a new liver-specific a-

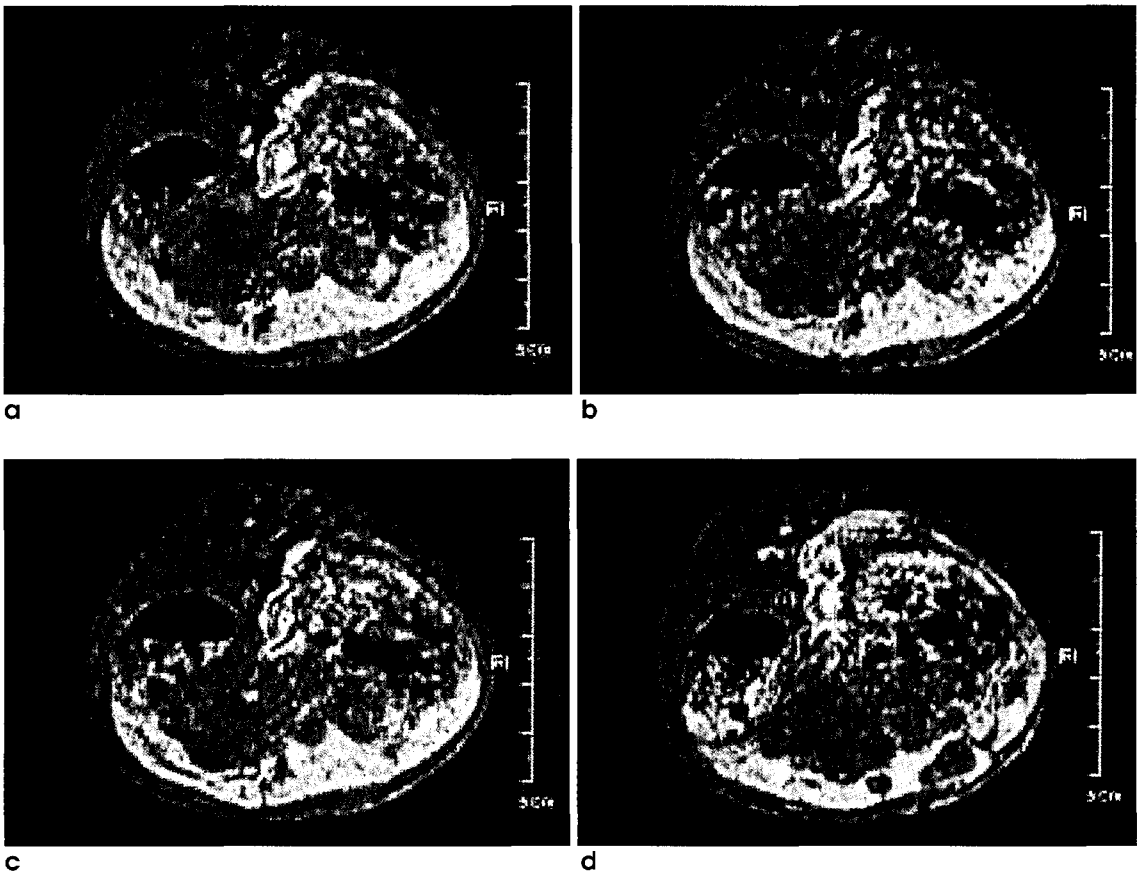

Fig. 6. FMPSPGR images (TR/TE = 516/14 msec) of Mn-DPDP in rabbit liver with experimentally implanted VX2 tumors. **a.** Before contrast agent. **b.** 8 minutes after intravenous injection of 0.01 mmol/kg Mn-DPDP. SI of the liver parenchyma and the tumor rim began to be increased. **c.** 29 minutes after injection. The increased signal enhancement of the liver parenchyma improved the visualization of the VX2 tumor lesion. **d.** 59 minutes after injection. No uptake of the contrast agent into the necrotic area was seen.

gent. Also, MnPC seems to be used as a dual contrast agent (T1 and T2) with high T2 relaxivity. That is, further characterizations of MnPC are needed in vivo and *in vitro* before clinical trials. The diagnostic potential of MnPC will also have to be examined more in the disease models of additional types.

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대한자기공명의과학회지 8:32-41(2004)

실험적으로 유발시킨 VX2 동물모델에서의 Mn-phthalocyanine과 Mangafodipir trisodium의 비교영상

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박현정[1] · 고성민[2] · 장용민[3] · 김용선[3]

목적 : MnPC의 자기이완성질을 살펴보고, 토끼의 간에 이식한 VX2 암종을 이용해 자기공명영상에서 간의 조영증강형태를 관찰하고자 하였다. 또한 간세포 특이성 조영제 사용 시와 비교하여 MnPC의 조직특이성 조영제로서의 가능성을 탐색해 보고자 하였다.

대상 및 방법 : 조영제 합성시 상자성 원소의 배위자로 phthalocyanine(PC)를 선택하였다. 2.01 g (5.2 mmol)의 phthalocyanine을 0.37 g (1.4 mmol)의 manganese chloride와 310℃에서 36시간동안 반응시킨 후 혼합물을 크로마토그래피(CHCl3: CH3OH=98:2, volume ratio)로 정제하여 2000 달톤의 분자량을 갖는 1.04 g (46%)의 MnPC를 얻었다. 자기이완율은 MnPC를 0.1 mmol로 희석시켜 1.5 T (64 MHz)에서 측정하였다. VX2 암종은 토끼의 간실질 내에 종양세포 부유액을 주입해 실험적으로 유발시켰다. 모든 영상은 1.5 T MR 장비에서 무릎관절코일을 사용하여 획득하였다. 본 연구에서 새로 개발된 거대분자 자기공명영상 조영제인 MnPC (4 mmol/kg)와 간세포 특이성 조영제인 Mn-DPDP (0.01 mmol/kg)가 사용되었으며 이들 조영제는 토끼의 이정맥을 통해 주입되었다. T1 강조영상은 스핀에코 (TR/TE=516/14 msec)와 고속다면회손경사회복 (TR/TE=80/4 msec, flip angle 60 °)을 사용하여 얻었고, T2 강조영상의 획득을 위해서는 고속스핀에코 (TR/TE=1200/85 msec)를 사용하였다.

결과 : MnPC의 1.5T (64MHz)에서의 자기이완율은 R1=7.28 $mM^{-1}S^{-1}$, R2=55.56 $mM^{-1}S^{-1}$ 이었고, MnPC의 높은 T2 자기이완율은 T2 강조영상에서의 정상 간실질의 신호강도를 감소시켜 간실질과 VX2 암종의 구분을 쉽게 하였다. MnPC 주입시 T1 강조영상에서는 간세포 특이성 조영제의 주입시보다 종양의 경계가 명확하였고, 조영증강은 주입 후 최소 한시간 이상 높게 유지되었다.

결론 : MnPC가 간세포로 흡수되어 담관으로 배설된다는 사실은 Mn-DPDP와 유사한 특성이며 이는 MnPC가 새로운 간특이성 조영제임을 확인시켜 준다. 또한 MnPC의 R2값이 기존의 조영제에 비해 매우 크다는 사실은 T1 조영제로서 뿐만 아니라 T2 조영제로서의 사용 가능성을 보여준다. 이러한 사실들을 좀더 정확하게 뒷받침하기 위해서는 임상적으로 사용되기 이전에 생체 내 그리고 시험관내 연구가 더 필요하며 다른 동물모델에서의 추가적인 연구가 요구된다.

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