Novel MR imaging contrast agents for detection of HT29/219 cells in mice

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Abstract:

New potential MR imaging contrast agents Gd-tetra-carboranylmethoxyphenyl-porphyrin (Gd-TCP) and Gd-hematoporphyrin (Gd-H) were synthesized and applied to mice with human colorectal (HT29/219) cells. A reduction (15% and 12%) in T_1 values was revealed 24 hrs after injection of the Gd-H and Gd-TCP. The percent of Gd that localized to the tumor was measured by UV spect to be 24 and 18% for Gd-H and Gd-TCP, respectively and was much higher compared with control ($GdCl_3$). Signal enhancement of 81 and 68% over the control was observed for Gd-H and Gd-TCP, respectively. The biodistribution finding allows quantitative studies of paramagnetic contrast agent uptake.

Introduction:

Gadolinium-porphyrins have been synthesized and are currently being investigated as MR imaging contrast agents (1, 2). Their high water solubility and stability under physiological conditions, low propensity for causing phtotoxicity, and intracellular localization in mitochondria for more efficient tumor cell killing, are reasons why these complexes have been used as new tumor-specific agents in MR imaging. An animal study was performed for developing pharmacokinetics of these contrast agents. The biodistribution, the T_1 relaxation times, and the signal enhancement of the contrast agents are presented and the results are compared.

Materials and Methods:

The synthetic porphyrin, 1,6,11,16-tetra(3-*o*-carboranylmethoxy)phenyl-porphyrin or Gd-TCP was produced by modification of the method of Miura *et al* and the naturally occurring porphyrin, hematoporphyrin IX was also inserted with Gd to yield Gd-H as both of those described previously (1,2). Solutions of $GdCl_3$, Gd-DTPA, and Gd-H were prepared by accurately dissolving the required amount in 0.9% saline solution. Gd-TCP was dissolved in 1 ml of cremophor (CRM) and 2 ml of 1,2-propanediol. This solution was transferred into a 10 ml volumetric flask, and a 0.9% saline solution was added to the mark. The animal studies were performed with mice of 6-8 week old with a mean weight of 25 g.

The colorectal cells, HT29/219 (2×10^6 cells), were injected subcutaneously in the both flanks of mice. Two weeks after tumor implantation, when the tumor diameter was 2-4 mm, mice were injected with the different contrast agents. The animals were sacrificed at 24 hr post IP injection followed by removal of critical organs (tumor, kidney, liver). Using acid digestion procedure according to the method of Tamat *et al* (3) the solution of samples was applied for both NMR and UV-spect experiments.

The T_1 relaxation times and signal intensities of solution of samples was measured using an inversion recovery (IR) pulse sequence technique using a 11.4 T *Bruker instrument* (500 MHz, Tarbiat Modarres University, Iran). The values of echo time and repetition time were optimized for different solutions. The UV-spectrophotometer (Spectronic Gene Sys2, Spectronic Instrument) was used to measure the concentration of Gd, which did not uptake by tumors.

Results and Discussion:

Relaxivity values of Gd-porphyrins are approximately 4 times higher than Gd-DTPA. The reduction of T_1 relaxation times of 15 and 12% (Fig.1) and the percent of injected Gd that localized to the tumor measured by UV-spect was approximately 24 and 18% for Gd-H and Gd-TCP after 24 hr, respectively. Higher concentration of Gd was achieved compared with control indicating selective delivery of Gd-porphyrins to the tumor. These findings showed the possible application of porphyrin-based contrast agents for the detection of colorectal cells. Overall, with the satisfactory low levels of Gd in the liver and kidney and good tumor uptake, Gd-porphyrins have considerable promise for further diagnosis applications of MR imaging.

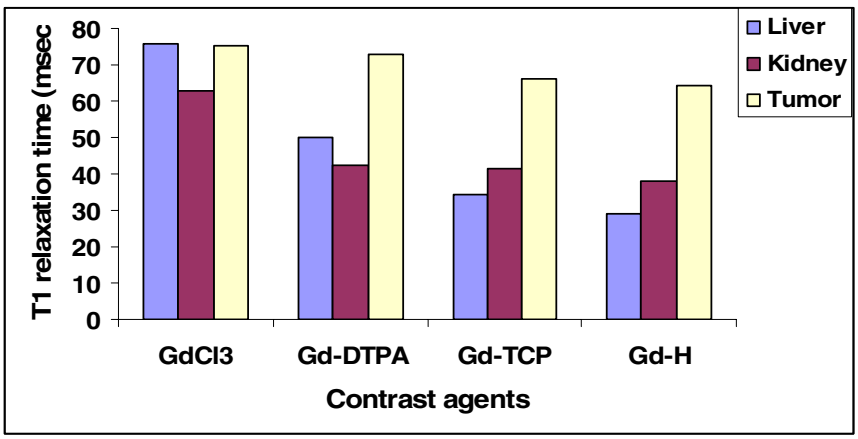

Fig. 1. T_1 relaxation times of different contrast agents in colorectal cells in mice after 24 hr.

References:

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