Evaluation of toxicity of gadolinium based contrast agents on skin fibroblasts

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Introduction:

Gadolinium based contrast agents have been reported to induce nephrogenic systemic fibrosis (NSF) in patients with impaired renal function. Skin fibrosis is a characteristic symptom while the mechanism of causing NSF is unclear. In this study, we investigated the cytotoxicty Gd(III)-based contrast agents, including Omniscan®, Mutihance® and ProHance®, to normal rat skin fibroblasts and effect of gadolinium(III) deposition and transmetallation on their cytotoxicity.

Materials and Methods:

The normal rat skin fibroblasts (from ATCC) were cultured in complete MEM medium. The cells were incubated with free gadolinium and gadolinium based contrast agents at various concentrations for 24 hours, and the cytotoxicity of the agents was determined by MTT assay. The cells receiving similar treatment were lysed and the Gd^{3+}, Ca^{2+}, Zn^{2+} and Mg^{2+} contents in lysates were determined by ICP-OES and normalized to protein concentration.

Results:

The gadolinium based contrast agents showed much lower cytotoxicity than free Gd^{3+} ions. When cultured with normal rat skin fibroblasts, 1 mM of free gadolinium resulted in only 25.1 +/- 9.8% of viability. Under the same condition, 1 mM contrast agents Omniscan, MultiHance and ProHance resulted in 105.4 +/- 2.7%, 85.4 +/- 1.9% and 96.2 +/- 1.1 % viability, respectively, Figure 1. With increased concentration in the medium, the contrast agents demonstrate higher cytotoxicity. The IC50 values are approximately 4.9 mM and 38.9 mM for MultiHance and Omniscan, respectively. ProHance showed much lower cytotoxicity than other agents, and 51.8+/1 3.6 % cell viability was stilled observed at a concentration as high as 100 mM. For all tested agents, the cellular deposits of Gd^{3+} increased with increased concentrations in medium, Figure 2. Transmetallation of the contrast agents was observed with intracellular Ca^{2+} and Zn^{2+} but Mg^{2+}. Omniscan with relatively low complexation stability leads to high intracellular Ca^{2+} accumulation at 50 mM in culture medium, Figure 4. Intracellular Zn^{2+} content decreased when exposed to the contrast agents, Figure 3. Omniscan at 50 mM deprived approximately 42% of intracellular Zn^{2+} ions.

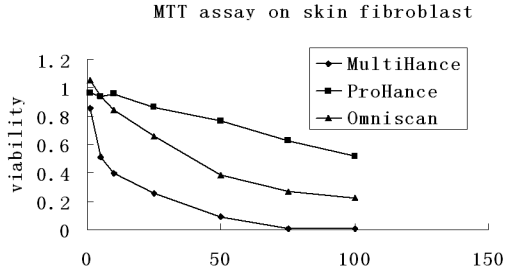

Figure 1

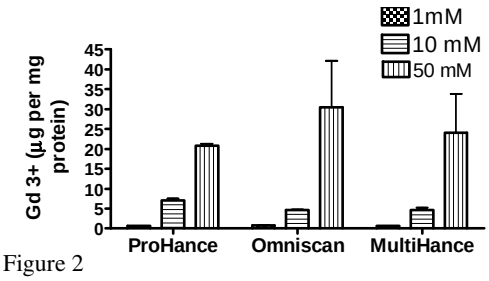

Figure 2

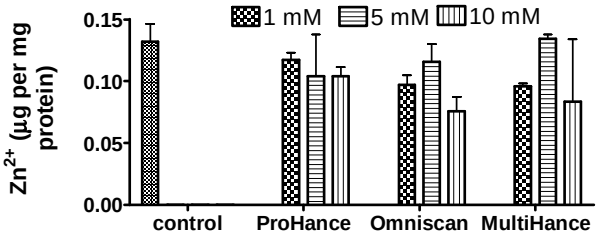

Figure 3

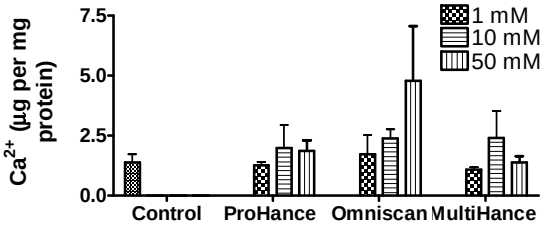

Figure4

Conclusions:

The gadolinium based contrast agents significantly decreased the cytotoxicity of Gd^{3+} ions to skin fibroblasts. The intracellular gadolinium deposit depended on contrast agent concentration. The intracellular Gd^{3+} deposition and Ca^{2+} and Zn^{2+} imbalance could be related to long-term toxicity of gadolinium based contrast agents on skin fibroblast. However, further study is required to understand the cause of NSF and role of Gd(III) based MRI contrast agents in NSF.

References:

Cowper SE et al, Lancet 356: 1000-1001, 2000