Gd-DTPA-Cystine diethyl ester copolymers

GDCEP

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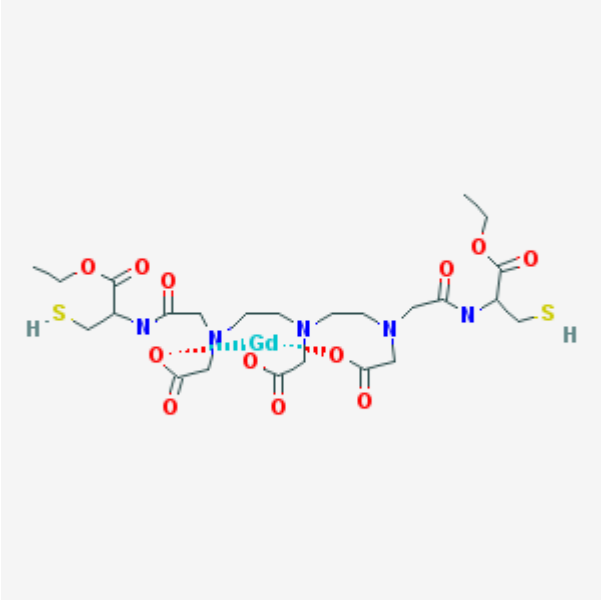
Chemical name:	Gd-DTPA-Cystine diethyl ester copolymers
Abbreviated name:	GDCEP
Synonym:	
Agent Category:	Compound
Target:	Non-targeted
Target Category:	Blood pool retention
Method of detection:	Magnetic resonance imaging, MRI
Source of signal \contrast:	Gadolinium, Gd
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

Magnetic resonance imaging (MRI) maps information about tissues spatially and functionally. Protons (hydrogen nuclei) are widely used to create images because of their

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abundance in water molecules. Water comprises about 80% of most soft tissues. The contrast of proton MRI depends mainly on the density of nuclei (proton spins), the relaxation times of the nuclear magnetization (T1, longitudinal; T2, transverse), the magnetic environment of the tissues, and the blood flow to the tissues. However, insufficient contrast between normal and diseased tissues requires development of contrast agents, which contain chemical moiety with unpaired electrons affecting the T1 and T2 relaxation times of the surrounding nuclei, predominantly the protons of water (1). MRI contrast agents work by shortening both T1 and T2 relaxation times of surrounding water protons to produce the signal-enhancing effect (2, 3), highlight vasculature, and delineate normal or nonmalignant tissues (4).

Gadolinium (Gd), a lanthanide metal ion with seven unpaired electrons, has been shown to be very effective in enhancing proton relaxation because of its high magnetic moment and water coordination (5, 6). Gd-Diethylenetriaminepentaacetate (Gd-DTPA) was the first intravenous MRI contrast agent used clinically, and a number of similar Gd chelates have been developed in an effort to further improve clinical use. However, these low molecular weight Gd chelates have short blood and tissue retention times, which limit their application as imaging agents in the vasculature and cancer. Various macromolecular Gd complexes have demonstrated superior contrast enhancement for MRI of the vasculature and carcinomas (4, 7, 8); however, these Gd complexes cannot proceed into further clinical development because of their slow excretion and high tissue accumulation of toxic Gd ions.

New, biodegradable, macromolecular Gd complexes, which can be readily degraded to smaller complexes for faster excretion through renal filtration, are being developed as MRI contrast agents (9). Gd-DTPA cystine copolymers (GDCP) and Gd-DTPA cystine diethyl ester copolymers (GDCEP) are biodegradable polydisulfide Gd(III) complexes that are readily degraded by a disulfide-thio exchange reaction (10-12). GDCP and GDCEP are being developed as contrast-enhanced MRI agents for use in blood pool and cancer imaging.

Synthesis

[PubMed]

Zong et al. (12) reported that the synthesis of GDCP and GDCEP consisted of two major steps. DTPA dianhydride was first copolymerized with cystine or cystine diethyl ester, and then complexed with $GdCl_3$ via DTPA to form GDCP and GDCEP, respectively. The yields of GDCP and GDCEP were 15% and 11%, respectively. The average molecular weight (M_W) of GDCP was 15.1 kDa; the average M_W of GDCEP was 10.2 kDa. The measured Gd contents in GDCP and GDCEP were 19.5% and 18.2%, respectively. The longitudinal T1 relaxivity (r_1) at 3T was 5.43 $mM^{-1}s^{-1}$ for GDCP and 5.86 $mM^{-1}s^{-1}$ for GDCEP.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Both GDCP and GDCEP rapidly degraded *in vitro* during incubation with a high concentration of cysteine (150 μM) at 37°C (12). Most of the copolymers degraded into smaller oligomers and complexes at 6 h, and eventually degraded to the smallest repeat unit of the copolymers, Gd-[DTPA-$(cysteine)_2$] and Gd-DTPA-[$(cysteine\ ethyl\ ester)_2$], as determined by mass spectroscopy. The r_1 of the degradation products of GDCP and GDCEP were 5.39 and 5.70 $mM^{-1}s^{-1}$, respectively. Compared with GDCP, GDCEP showed more rapid degradation into smaller units in rat blood plasma as in the presence of cysteine (11). About 10% of GDCP degraded into smaller GD complexes in 6-h incubation, while >60% of GDCEP degraded in 1-h incubation. Little free Gd was detected.

Animal Studies

Rodents

[PubMed]

In mice and rats, GDCP and GDCEP rapidly distributed into the blood and vascular compartments, and both showed a marked affinity for renal excretion (10-12). The biodistribution study showed that both were found mainly in the liver, kidneys, spleen, and heart. GDCP and GDCEP degradation was confirmed in the urinary samples of rats. Pharmacokinetic studies of GDCEP, GDCP, and the nondegradable macromolecular copolymer Gd-DTPA-1,6-hexanediamine copolymer (GDHC) (0.1 mmol/kg) were conducted in rats by Feng et al. (10), who found that the blood kinetics [distribution half-life ($t_{½}$), α; elimination $t_{½}$, β] were 1.60 ± 0.73 min (α) and 29.3 ± 15.9 min (β), 3.15 ± 1.26 min (α) and 33.1 ± 19.3 min (β), and 5.92 ± 2.02 min (α) and 222.6 ± 63.9 min (β), for GDCP, GDCEP, and GDHC, respectively. The rank order of blood retention was GDHC>>GDCP>GDCEP, which corresponded to the degrees of nondegradation of the copolymers. The α phase of GDCP was significantly longer than that of GDCEP ($P < 0.05$). The accumulation of GDHC in the muscle, liver, kidney, and spleen was higher than that of GDCP and GDCEP, and GDCP exhibited significantly higher accumulation in these organs than did GDCEP. GDHC showed stronger and more prolonged contrast enhancement than GDCP and GDCEP in the heart and blood vessels in MRI, and GDCP showed longer enhancement duration than GDCEP. On the other hand, GDCP and GDCEP exhibited more significant enhancement in the kidneys than GDHC.

Zong et al. (12) studied MRI using GDCP and GDCEP (0.1 mmol/kg) in nude mice bearing MDA-BM-231 human breast carcinoma xenografts. Gd-DTPA-BMA (bis(methyl)amide), a low molecular weight Gd complex, was used as a control. GDCP and GDCEP resulted in strong contrast enhancement in the blood pool at 5 min after injection. Some blood vessels connected to tumor tissue were clearly visible with both

agents. Significant contrast enhancement in the tumor tissues (predominantly in the periphery) was also observed. The tumor contrast enhancement for GDCP rapidly declined after 5 min, and only minimal contrast enhancement was observed at 15 min after injection. The contrast enhancement with GDCEP decreased more gradually in the blood pool, such that significant contrast enhancement was still present at 60 min after injection. No significant contrast enhancement was observed for Gd-DTPA-BMA at 5 min after injection or thereafter.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

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