Dimeric Gd-tetraazacyclododecanetetraacetic acid-folate

P866

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Chemical name:	Dimeric Gd-tetraazacyclododecane-tetraacetic acid-folate	
Abbreviated name:	P866	
Synonym:		
Agent category:	Compound	
Target:	Folate receptor	
Target category:	Receptor	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal:	Gadolinium, Gd	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available in PubChem.

Background

[PubMed]

Folic acid (folate) is a water-soluble B vitamin (1) essential for methylation and DNA synthesis. The primary pathway for entry of folate into cells is with the facilitated transporter folate-binding protein (FBP), which has a low affinity for folate with a K_m value of 1–5 μM. Some cells in the choroid plexus, kidney, lung, thyroid, spleen, placenta, and thymus also possess a high-affinity receptor (dissociation constant (K_d), 0.5 nM) that allows folate retention *via* receptor-mediated endocytosis. Some human epithelial tumor cells have been found to overexpress FBP (2). More than 90% of human ovarian and endometrial cancers express the high-affinity folate receptor, which is absent in normal

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tissues. Breast, colorectal, renal, and lung carcinomas also overexpress the folate receptor but to a lesser frequency (20–50%).

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 (3, 4). Gd-Labeled diethylenetriaminepentaacetic acid (Gd-DTPA) was the first intravenous magnetic resonance imaging (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 use as imaging agents in the vasculature and cancer; furthermore, they are largely nonspecific. P866 is composed of folic acid coupled to a high-relaxivity dimeric Gd-tetraazacyclododecane-tetraacetic acid (Gd-DOTA) derivative. P866 has been studied as a MRI agent for folate receptor expression in nude mice bearing human cancer xenografts and in rats with arthritis (5-7).

Synthesis

[PubMed]

P866 is commercially available (Guerbet Research, Paris, France) and has a molecular weight of 9.4 kDa with two Gd-DOTA moieties and one folic acid molecule per P866 molecule (7). P1001 is composed of the two Gd-DOTA moieties without folic acid. The r1 and r2 relaxivities of P866 and P1001 are ~21 and ~30 $mmol^{-1}s^{-1}$ in water at 60 MHz and 37°C, respectively. On the other hand, the r1 and r2 relaxivities of Gd-DOTA are 3.1 and 3.7 $mmol^{-1}s^{-1}$ in water at 60 MHz and 37°C, respectively.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Corot et al. (6) performed binding experiments with P866 and folic acid with use of a Biacore sensor chip immobilized with FPB. The K_d value of P866 was calculated to be 26.7 μM, and the K_d value of folic acid was 10.0 μM. Using *in vitro* binding experiments on KB tumor cells, [^{3}H]folic acid bound to a single site with a K_d value of 0.9 nM and a maximal binding value of 7 million folate receptor binding sites/cell. The 50% inhibition concentration values were 5.9 and 59.3 nM for folic acid and P866, respectively. After incubation of 80 uM P866 on KB tumor cells for 2 h, the r1 relaxivity for tumor cells was 19.6 $mmol^{-1}s^{-1}$, which was 22% lower than that for tumor cells alone. Co-incubation with excess folic acid abrogated the change in the r1 relaxivity induced by P866 as well as the reduction of Gd concentration in the KB cells by ~90%. HT1080 (negative for the folate receptor) tumor cells showed little change in the r1 relaxivity after incubation with P866.

Animal Studies

Rodents

[PubMed]

Using an antigen-induced arthritis model in rats (n = 15), Saborowski et al. (7) showed that T1 relaxation times of the synovitis at 2 h after injection with P866 (0.02 mmol/kg) was significantly shortened ($P < 0.05$) with little change in T1 relaxation times in the normal joint. On the other hand, injection with P1001 (0.02 mmol/kg) or Gd-DOTA (0.01 mmol/kg) induced little change in T1 relaxation times in the synovitis. The blood half-lives were 19.4, 28.8, and 31.0 min for P866, P1001, and Gd-DOTA, respectively. Autoradiography studies of tissue sections showed a four-fold higher amount of folate receptor in the arthritic joint as compared with the normal joint. Histoimmunological staining showed that infiltrating lymphocytes and macrophages in the arthritic joint were positive for folate receptors.

Corot et al. (6) performed 2.4-T MRI studies for 4 h in mice bearing human KB tumor xenografts with 0.015 mmol/kg P866 and P1001. There was a significant increase ($P < 0.05$) in tumor T1w maximum enhancement in the KB tumors for P866 (n = 7 mice, 42 ± 18%) over P1001 (n = 6 mice, 25 ± 14%). Biodistribution studies were also performed (n = 3 mice/group) at 1, 4, and 24 h after injection, with tumor Gd levels of 3.2, 2.7, and 2.1% injected dose/g, respectively. The tumor/muscle ratios were 2.2, 5.1, and 4.0 at 1, 4, and 24 h after injection, respectively. Co-administration of folic acid (0.1 mmol/kg) inhibited the binding by 27, 49, and 49% at 1, 4, and 24 h after injection, respectively.

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.

References

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