Copper 1,4,8,11-tetraazacyclotetradecane-*N,N',N'',N'''*-tetraacetic acid-octreotide

Cu-TETA-OC

The MICAD Research Team

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Chemical name:	Copper 1,4,8,11-tetraazacyclotetradecane-N,N',N",N'"-tetraacetic acid-octreotide
Abbreviated name:	Cu-TETA-OC; ^{64}Cu-TETA-OC; ^{64}Cu-TETA-octreotide; ^{64}Cu-TETA-OC
Synonym:	
Agent Category:	Compound
Target:	Somatostatin receptor
Target Category:	Binding of the octreotide
Method of detection:	PET
Source of signal:	^{64}Cu
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates • Humans

Background

[PubMed]

Somatostatin is a tetradecapeptide acting as an inhibitor of the release of somatotropin, glucagon, gastrointestinal hormones, and other secretory proteins. The targeting of somatostatin receptors with radiolabeled peptides has led to the development of a variety of agents for both diagnostic imaging and radiotherapy of somatostatin receptor-positive tumors, an area of cancer research where considerable progress has been made over the last few years.

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^{64}Cu-TETA-octreotide (or ^{64}Cu-TETA-OC) is a somatostatin receptor showing high affinity for binding, both *in vitro* and *in vivo* (1). Its high rate of lesion detection, favorable dosimetry, and clearance properties make it a promising agent for positron emission tomography (PET) imaging of neuroendocrine tumors in patients (2). ^{64}Cu -TETA-OC displays a similar affinity as ^{111}In-DTPA-octreotide, a clinically approved imaging agent for somatostatin receptor-positive tumors.

Several animal studies also showed the therapeutic value of ^{64}Cu-TETA-OC as a tumor growth inhibitor (3). The mechanism of the tumor cell killing process is still unclear and currently under investigation (4). Preliminary subcellular distribution studies suggest a possible role played by the localization of ^{64}Cu to the tumor cell nuclei, a result from the dissociation of the metal from macrocyclic chelators *in vivo* (5) , followed by trafficking of the radiometal to the cell nuclei (4).

Synthesis

[PubMed]

TETA-OC can be prepared following a procedure by Anderson et al. (3). Briefly, the OC is protected with a tert-butoxycarbonyl (Boc) group by reaction with $(Boc)_2O$ in Me_2SO, and TETA·4HCl·4H_2O is neutralized with 4.5 equivalents of aqueous LiOH. The N-terminal amine of Boc-protected OC is conjugated to one of the carboxylic acid moieties on TETA with HBTU in Me_2SO, using di-isopropylethylamine and hydroxybenzotriazole as catalysts.

^{64}Cu-TETA-OC can be synthesized using the method described by Bass et al. (6). This procedure involves diluting $^{64}CuCl_2$ with 0.1 M NH_4OAc, at pH 5.5, then adding to TETA-OC and adjusting the final volume to 1.0-1.5 ml with buffer. After a 60-min incubation at room temperature, ^{64}Cu-TETA-OC is purified using a Sep-Pak cartridge (7). By following this procedure, the radiochemical purity of ^{64}Cu-TETA is >90%, and the radiochemical purity of ^{64}Cu-TETA-OC is >95% (by high-performance liquid chromatography, HPLC) (8).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro studies on somatostatin receptor-positive AR42J rat pancreatic tumors and focused on the subcellular distribution of ^{64}Cu -TETA-OC showed a localization of substantial quantities of ^{64}Cu to the cell nucleus and mitochondria (4). This process was shown to be a main contributing factor in the tumor cell killing process (4). It was also suggested that the instability of the moiety of ^{64}Cu-TETA under biological conditions was the cause of the translocation of ^{64}Cu to the nucleus.

Wang et al. (4) observed that the majority of ^{64}Cu-TETA-OC was internalized in AR42J cells by receptor-mediated endocytosis. This internalization process increased steadily over a 24-h time period, with low amounts of cell surface-associated activity, suggesting a rapid turnover and recycling of SSTR2 receptors.

Using a procedure modified from the one by Zinn et al. (9), Wang et al. (4) showed that the percentage of surface-bound, cell-associated activity ranged from almost 7% to >16%, with the amount of surface-bound activity increasing at 24 h, and that the majority of ^{64}Cu-TETA-OC was internalized.

Animal Studies

Rodents

[PubMed]

^{64}Cu-TETA-OC was shown to inhibit the growth of somatostatin receptor-positive tumors in rats at doses exhibiting minimal toxicity. In one study, Anderson et al. (3) performed experiments on rats bearing palpable CA20948 pancreatic tumors by injecting them with either a single 15-mCi dose, a fractionated amount of 15 mCi given in two to three doses over 2-8 days, or control agents of buffer OC. Results showed that ^{64}Cu-TETA-OC could greatly inhibit the growth of pancreatic tumors at doses causing minimal toxicity. The only toxicity observed in treated rats was a decrease in the white blood cell count, a significant drop for rats treated by single injection, and a slight decrease (with rebound) for those receiving a fractionated dose treatment. Injection of fractionated doses appeared to be more effective than a single dose treatment, showing a 25% reduction in tumor growth rate compared with single-dose injections (and a 75% reduction for the buffer control group). Estimated absorbed doses of ^{64}Cu-TETA-OC to the tumor were between 465 and 540 rads. At those doses, tumor inhibition—and even tumor regression (for large tumors)—was observed; however, all tumors eventually re-grew.

Using a model of tumor-bearing Lewis rats, the estimated human absorbed doses to normal organs showed the bladder wall (1.12 rad/mCi) and the lower large intestine (0.86 rad/mCi) to be the primary and secondary critical organs; the human effective dose equivalent was found to be 0.21 rad/mCi (3). ^{64}Cu-TETA-OC and ^{111}In-DTPA-OC showed similar biodistributions in tumor-bearing rat models (7).

Rat studies performed by de Jong et al. (10) showed that altering the OC structure slightly (by substitution of a tyrosine for phenylalanine, for example) resulted in a better uptake of the peptide in receptor-rich tissues such as adrenals, pancreas, pituitary, and tumor. However, rat studies showed retention of the activity of ^{64}Cu-TETA-OC in the blood, liver, and bone marrow, suggesting a possible dissociation of ^{64}Cu from TETA *in vivo*. In their study, Bass et al. (6) showed that ^{64}Cu dissociated from ^{64}Cu-TETA-OC and bound to proteins in large concentrations, such as superoxide dismutase (6).

Other Non-Primate Mammals

[PubMed]

No reference currently available.

Non-Human Primates

[PubMed]

PET imaging studies using ^{64}Cu-TETA-OC have been performed using non-human primates to estimate human absorbed doses. Data obtained by Anderson et al. (2) for ^{64}Cu-TETA-OC PET imaging on baboons showed the dose-limiting organs to be the bladder wall (0.62 rad/mCi), followed by the kidneys (0.49 rad/mCi). The estimated human absorbed dose for the total body was found to be 0.07 rad/mCi. The large discrepancy between dosimetry in rats and baboons obtained for the intestinal absorbed doses was explained by the very different excretion patterns of these animals.

Human Studies

[PubMed]

Human absorbed doses of ^{64}Cu-TETA-OC to normal organs were estimated from biodistribution data in both tumor-bearing Lewis rats and baboons (2) (see sections on rodents and non-human primates).

Anderson et al. (2) performed ^{64}Cu-TETA-OC PET studies on eight patients with histologically proven neuroendocrine tumors (five with carcinoid tumors of the gastrointestinal tract and three with pancreatic islet cell tumors). Pharmacokinetic analysis of blood samples obtained from patients showed that ^{64}Cu-TETA-OC PET cleared rapidly from the blood. However, 7.9 ± 3.7% injected dose (ID) remained (range, 3.2-13.5 %ID) 4 h after injection. The activity decreased further from 6 to 22 h, with amounts ranging from 0.8 to 6.6 %ID (mean, 3.3 ± 2.3%ID). Large variations were observed from patient to patient. Similarly to the results obtained in rat studies, ^{64}Cu was retained in the blood, and ^{64}Cu-TETA-OC did not completely clear from the circulation (7).

Comparative studies between ^{64}Cu-TETA-OC PET and ^{111}In-DTPA-OC scintigraphy showed that, in general, more lesions were detected using ^{64}Cu-TETA-OC because of the higher resolution obtained with PET imaging. Nevertheless, the image quality was in some cases superior by using DTPA because of the absence of intense activity in the bladder and kidneys when using ^{111}In-DTPA-OC (2).

References

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