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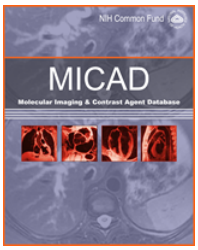

[^{166}Ho]-Loaded poly(L-lactic acid) microspheres

[^{166}Ho]-PLLA-MS

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Chemical name:	[^{166}Ho]-Loaded poly(L-lactic acid) microspheres	
Abbreviated name:	[^{166}Ho]-PLLA-MS	
Synonym:	[^{166}Ho]-PLA-MS	
Agent Category:	Compound	
Target:	Hepatic arterioles	
Target Category:	Arterioles	
Method of detection:	Multimodality imaging: Magnetic resonance imaging (MRI); single-photon emission computed tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	^{166}Ho	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals	Structure not available in PubChem.

Background

[PubMed]

Hepatic metastases often occur in individuals having breast, colorectal, or neuroendocrine neoplastic tumors and usually indicate a poor prognosis for the patient (1). Radiotherapy or partial hepatectomy are often used for the treatment or removal of the hepatic tumors, respectively, but only 20%–30% of patients are eligible for these procedures because large or widespread lesions may occur in the organ or the patient may not benefit from either treatment due to the disease being at an advanced stage. In addition, many patients do not respond to the chemotherapeutic drugs used for the treatment of these lesions and suffer from many side effects as a result of the nonspecific cytotoxic or cytostatic activities exhibited by these drugs (1). Radioembolization of the tumors with ^{90}Y-embedded microspheres (MS) were developed as an alternative treatment for this malignancy; ^{90}Y is a pure high-energy β-emitter but exhibits low tissue penetration (2). This technique involves the placement of radioactive MS into the hepatic artery of the patient through a catheter; the infused MS travel to and are lodged in the tumor arterioles (the blood supply to hepatic tumors is primarily from the hepatic artery *versus* the hepatic portal vein for normal liver tissue) (3). Delivery of the high-energy β radiation from the MS within the tumor then proves fatal for the tumor cells. However, although this is considered to be a safe and suitable

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method for the treatment of hepatic malignancies, its main drawback is that after infusion into the artery, due to the low tissue penetration of the β radiations, the biodistribution of ^{90}Y-embedded MS cannot be visualized accurately with nuclear imaging (1). The United States Food and Drug Administration has approved >100 clinical trials to evaluate MS (with or without radionuclides) for the treatment of various diseases including cancers.

To visualize and treat hepatic neoplastic lesions, poly(L-lactic acid) microspheres loaded with radioactive holmium-166 (half-life = 26.8 h; [^{166}Ho]-PLLA-MS) were developed (2). A characteristic feature of ^{166}Ho is the dual emission of β and γ particles (~94% and ~6%, respectively, of the total radioactivity), making it a suitable nuclide for radioembolization or visualization of the biodistribution of the MS with single-photon emission computed tomography (SPECT) imaging (4). In addition, ^{166}Ho is highly paramagnetic and can be detected easily in the tissue with magnetic resonance imaging (MRI). Also, the ^{166}Ho-loaded MS can be easily produced under Good Manufacturing Practice conditions (4). The biodistribution of [^{166}Ho]-PLLA-MS has been investigated in rat models (5), rabbit models (with SPECT (6) and MRI (7)), and porcine models (with SPECT *in vivo* and MRI *ex vivo* (8)). The design of a phase I clinical trial using escalating doses of ^{166}Ho-PLLA-MS for the treatment of patients with liver metastases was published recently by Smits et al. (1).

Synthesis

[PubMed]

The synthesis of [^{166}Ho]-PLLA-MS was described by Nijsen et al. (2). Characterization of the MS was performed with scanning electron microscopy, laser particle size analysis, and γ-spectrometry. The particles were reported to incorporate ~17.0 ± 0.6% ^{166}Ho (w/w; n = 5) and were 20–50 μm in diameter. To obtain the best yield of the radiochemical the investigators concluded that non-radioactive [^{165}Ho]-PLLA-MS should be free of water and that the high neutron flux and irradiation time of the MS should be < 1 h. The specific activity of [^{166}Ho]-PLLA-MS was reported to be 75 MBq/mol (2.025 Ci/mol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

On incubation of the [^{166}Ho]-PLLA-MS in phosphate-buffered saline (PBS; pH not reported) or pig liver homogenate at 37°C for 288 h, some morphological changes were visible in the labeled MS (2). However, the MS retained >98.0% of ^{166}Ho even after 192 h incubation in PBS, plasma, leukocytes, and liver homogenate under these conditions.

Almost no degradation of the [^{166}Ho]-PLLA-MS was observed when exposed to human serum for >380 h, and the spheres retained >97% of the radioactivity during this time (6).

Mumpher et al. detected [^{166}Ho]-PLLA-MS in hematoxylin-eosin–stained rabbit liver sections 1 h after administration of the tracer (6). The MS were shown to have accumulated mainly in the arteries and arterioles of the organ.

Nijsen et al. showed that MRI can be used to track the movement of [^{166}Ho]-PLLA-MS in rabbit livers *ex vivo* (7). This study showed that the MS initially accumulated in the small blood vessels of the liver and thereafter in the larger blood vessels of the liver.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{166}Ho]-PLLA-MS was investigated in rats implanted with medullary thyroid carcinoma tumors in the liver (5). The tumor-bearing animals were injected with the labeled MS with (n = 9 animals) or without (n = 6 animals) adrenaline treatment as described (5). Adrenaline is well known to increase blood flow in the liver. Control animals (n = 6 rats) had a sham implantation and were injected with the labeled MS in a similar manner. The animals were subjected to whole-body SPECT imaging using a gamma camera at 30 min and 1 day after administration of the tracer. The animals were subsequently euthanized for removal of the tumors and the major organs to determine the amount of radioactivity incorporated in the tissue. All data were presented as percent of injected dose per gram tissue (% ID/g). No significant difference in the incorporation of radioactivity was observed between animals with or without the adrenaline treatment. Approximately 37.5 ± 22.5% ID/g tracer was observed to have accumulated in the hepatic tumors of the test animals compared to ~5.0 ± 3.5% ID/g at the sham implantation site for the control animals. In general, the incorporation of radioactivity in the major organ tissues in both the experimental and the control animals ranged from <0.1% ID/g to 0.4% ID/g. A significantly (P < 0.001) higher tumor/non-tumor (T/N) tissue ratio (6.1 ± 2.9) was determined in the tumor-bearing rats compared to a T/N tissue ratio of 0.7 ± 0.5 in the sham-implanted controls. The radioactivity was confined primarily in the tumor and in the liver lobe with the implanted tumor in the tumor-bearing rats. Consequently, the T/N ratio of tumor was significantly (P = 0.003) reduced to 4.0 ± 1.6 if only the tumor-implanted lobe of the liver was taken as the non-target region to derive the ratio instead of the whole liver.

Whole-body gamma planar imaging showed that >95% of the tracer accumulated in the tumor and the liver, and there was almost no redistribution of radioactivity over time.

Other Non-Primate Mammals

[PubMed]

To study the biodistribution and *in vivo* stability of [^{166}Ho]-PLLA-MS, six anesthetized healthy New Zealand rabbits were injected with the labeled MS through the hepatic portal vein (6). Scintigraphic images acquired every 24 h from the animals showed that the liver outlines were uniformly defined and that there was negligible leaching of radioactivity from the organ. At 144 h after administration, 92.1 ± 4.7% ID/g of the tracer had accumulated in the liver followed by kidneys (1.2 ± 0.7% ID/g) and the femur (0.8 ± 0.5% ID/g). All other major organs had an accumulation of <0.2% ID/g.

In another study, four rabbits with tumors implanted in the liver were treated with approximately 50 mg (~ 640 MBq) of [^{166}Ho]-PLLA-MS and gamma planar and MRI images were subsequently acquired from these animals (7). This study demonstrated that MRI could detect the radioactive, non-radioactive, and decayed [^{166}Ho]-PLLA-MS for the entire time during which the MS stayed in the body. In addition, MRI could detect accumulation of the labeled MS in and around the hepatic tumors, and this observation was confirmed with whole-body gamma planar imaging three days after injection of the labeled MS. Results from this investigation indicated that MRI could be used to image [^{166}Ho]-PLLA-MS therapy under *in vivo* conditions (7).

A scout and a treatment dose of [^{166}Ho]-PLLA-MS administered to five healthy pigs through the hepatic portal artery were shown to be accurately measured qualitatively and quantitatively with SPECT (9). In addition, MRI was shown to detect low doses of the labeled MS given to the animals. From this study, the investigators concluded that the ^{166}Ho-labeled MS could be detected easily in large animals using either SPECT or MRI techniques.

Non-Human Primates

[PubMed]

No publications are currently available.

Human Studies

[PubMed]

No publications are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

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