^{177}Lu-Labeled methylene diphosphonate

[^{177}Lu]-MDP

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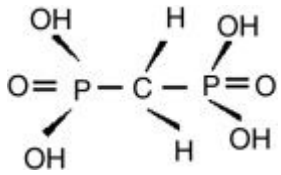
Created: May 24, 2011; Updated: June 30, 2011.

Chemical name:	^{177}Lu-Labeled methylene diphosphonate
Abbreviated name:	[^{177}Lu]-MDP
Synonym:	
Agent Category:	Compound
Target:	Type 2 class of aminoacyl-tRNA synthetases
Target Category:	Enzyme
Method of detection:	Single-photon emission tomography (SPECT); gamma planar imaging
Source of signal / contrast:	^{177}Lu
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of methylene diphosphonate.

Background

[PubMed]

Most patients with malignancies of the breast, prostate, lungs, thyroid, or kidneys suffer from severe bone pain due to metastases of the cancer in the skeletal tissue (1, 2). Although several interventions such as analgesics, bisphosphonates, hormone therapy, and systemic radionuclide therapy are available to manage bone pain, these treatments are known to have many undesirable secondary effects on the patient (2). Radiopharmaceuticals containing nuclides such as strontium-89 (as $^{89}SrCl_2$) and samarium-153 (administered as ^{153}Sm-labeled ethylenediamine tetramethylene

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NLM Citation: Chopra A. ^{177}Lu-Labeled methylene diphosphonate. 2011 May 24 [Updated 2011 Jun 30]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

phosphonic acid (EDTMP)), which have been approved by the United States Food and Drug Administration (FDA) for the treatment of bone pain due to metastases, are commonly used for the palliative care of bone pain in cancer patients (2). However, these are not ideal agents to treat bone pain because the radionuclide either has a long half-life and generates high-energy β^- particles (^{89}Sr has a half-life of ~50 days; $E_{\beta(max)}$ = 1.49 MeV) or is short-lived and has to be produced in close vicinity to the treatment center (^{153}Sm has a half-life of ~47 h; $E_{\beta(max)}$ = 0.81 MeV; $E\gamma$ = 103 keV (28%)) (1). A major limitation of using these bone pain palliative agents is that they produce myelotoxicity in some patients (3). Between the two labeled compounds, $^{89}SrCl_2$ appears to be the agent of choice for clinical applications because its longer half-life allows some flexibility to develop a suitable treatment regimen for the patient. There is great interest in the development of alternative radiolabeled compounds that can be used to treat pain resulting from osseous metastases (2). An important characteristic of a new labeled compound is that it must have the ability to be targeted specifically to the cancerous lesions on the skeleton and should be minimally toxic to the bone marrow as discussed elsewhere (3-5).

In a study with healthy rats, it was reported that EDTMP labeled with lutetium-177 ([^{177}Lu]-EDTMP) was cleared rapidly from blood circulation, showed little uptake in the soft tissues, and accumulated primarily in the bones of these animals (6). Chakraborty et al. made similar observations when they investigated the biodistribution of [^{177}Lu]-EDTMP in rats (7), and a freeze-dried kit for the preparation of this radiopharmaceutical has also been developed (8). On the basis of these observations, there is a renewed interest to use ^{177}Lu (half-life, ~7 days; $E_{\beta(max)}$ = 497 keV; $E\gamma$ = 113 keV (6.4%); 208 keV (11%)) as an alternative nuclide to those currently in use (^{89}Sr and ^{153}Sm) in the development of a palliative care agent for pain due to the metastases of cancer to the skeletal tissue (4, 5). The main advantages of using ^{177}Lu are that it can be easily transported to places where it is not available, and the low-energy gamma photons emitted by the nuclide allow detection of the bone lesions with scintigraphy. The International Atomic Energy Agency has initiated projects to develop ^{177}Lu-labeled compounds as palliative care agents for bone pain (5).

Methylene diphosphonate (MDP; also known as methylene diphosphate) labeled with technetium-99m is a commonly used bone-imaging agent approved by the FDA to investigate osteogenesis, and it is commercially available in the form of a kit (9). Because of its easy availability, and on the basis of the information mentioned above, Abbasi developed ^{177}Lu-labeled MDP ([^{177}Lu]-MDP) as a possible alternate radiopharmaceutical for the palliative care of bone pain (10). The biodistribution of this tracer was studied in Sprague-Dawley rats and confirmed with gamma planar imaging.

Other Sources of Information

Methylene diphosphonate (MDP)-related chapters in MICAD

Clinical trials with MDP and related compounds (with or without radionuclide labeling)

Clinical trials for bone pain treatment

Rat aminoacyl tRNA synthetase protein and mRNA sequences

Gene information regarding rat aminoacyl-tRNA synthetase (GeneID: 114632) (Source: Entrez Gene)

Aminoacyl tRNA synthetase in Online Mendelian Inheritance in Man (OMIM)

Structure of human cytosolic phenylalanyl tRNA synthase (Source: NCBI)

Bone palliative agents on the FDA site

FDA-approved clinical trials with EDTMP, $^{89}SrCl_2$, and ^{153}Sm complexes

Clinical trials with other bone-imaging agents

Synthesis

[PubMed]

A freeze-dried kit of MDP was used to optimize the production of [^{177}Lu]-MDP as described by Abbasi (10). The efficiency of the labeling reaction and the radiochemical purity of the final product were both >99% as determined with thin-layer chromatography. The R_f values for [^{177}Lu]-MDP and $^{177}LuCl_3$ were reported to be 0.82 ± 0.04 and zero, respectively, as determined with paper chromatography. Specific activity of the radiolabeled compound was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* stability of [^{177}Lu]-MDP was determined by incubating the tracer at room temperature from 1 min to 92 h as described by Abbasi (10). The labeled compound was reported to have 100% stability for ~22 h, which decreased to ~80% by 92 h. Stability of the probe in rodent or human serum under *in vitro* conditions was not reported.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{177}Lu]-MDP was studied in Sprague-Dawley rats (n = 3 animals/time point) as detailed elsewhere (10). The animals were given an intravenous injection of the tracer (~18.5 MBq (~0.5 mCi)) and euthanized at predetermined time points from 2 min to 22 h. Accumulated radioactivity in the major organs, including the femur, was measured as described, and the data were presented as percent uptake of injected dose per gram tissue (% ID/g). The accumulation of radioactivity in the femur increased from 0.56

± 0.02% ID/g at 1 h postinjection (p.i.) to 1.33 ± 0.04% ID/g at 2 h p.i. and 2.26 ± 0.02% ID/g at 22 h p.i. During this period, the liver showed a nearly constant level of radioactivity (~6.3% ID/g), and the tracer level in the lungs decreased from 31.63 ± 0.97% ID/g at 1 h p.i. to 1.3 ± 1.06% ID/g at 22 h p.i. In the kidneys, accumulation of the probe decreased from 0.51 ± 0.06% ID/g at 1 h p.i. to 0.25 ± 0.05% ID/g at 22 h p.i. The total uptake in the skeleton was calculated to be 8.18 ± 0.05% ID at 1 h p.i. and increased to 31.29 ± 1.27% ID at 22 h p.i. (see calculation details in Abbasi (10)).

Gamma planar imaging of anesthetized rats (n = 2 animals) at 22 h p.i. confirmed that the radioactivity was present primarily in the skeletal tissue of the rodents, followed by the liver as observed during the biodistribution studies (10).

From this study, the investigators concluded that [^{177}Lu]-MDP accumulated mainly in the skeletal tissue of the rats, and, except in the liver, little uptake was observed in other soft tissue (10).

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.

Supplemental Information

[Disclaimers]

No information is currently available.

References

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