^{68}Ga-Labeled 2-[4,7-di(carboxymethyl)-1,4,7-triazonan-1-yl]-5-[(4-hydroxy-4,4-diphosphonobutyl)amino]-5-oxopentanoic acid (NOTA-bisphosphonate (BP))

[^{68}Ga]-NOTA-BP

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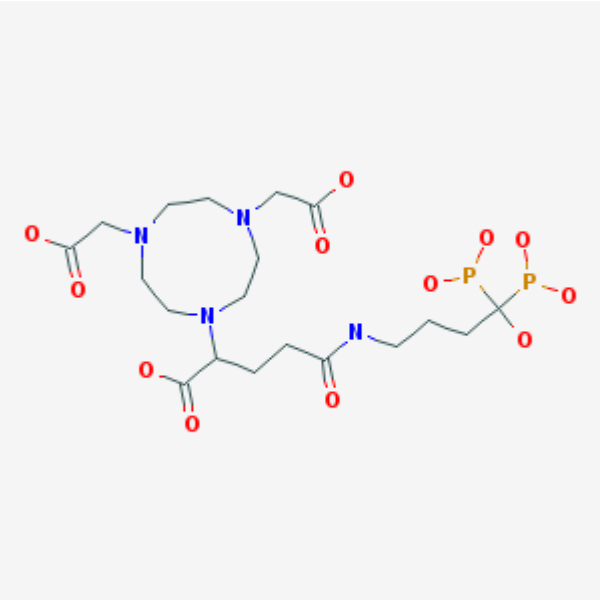
Chemical name:	^{68}Ga-Labeled 2-[4,7-di(carboxymethyl)-1,4,7-triazonan-1-yl]-5-[(4-hydroxy-4,4-diphosphonobutyl)amino]-5-oxopentanoic acid (NOTA-bisphosphonate (BP))
Abbreviated name:	[^{68}Ga]-NOTA-BP
Synonym:	[^{68}Ga]-NOTA-bisphosphonate
Agent Category:	Compound
Target:	Bone (hydroxyapatite) at low concentration; farnesyl disphosphate (pyrophosphate) synthase (molecular target) at high concentration
Target Category:	Other (tissue); enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal / contrast:	^{68}Ga
Activation:	No



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Studies:	• *In vitro* • Rodents	Click on above structure for information in PubChem.

Background

[PubMed]

Bisphosphonates (BPs; also known as diphosphonates), such as methylene diphosphonate (MDP) and zoledronic acid, can be labeled with technetium-99m ([^{99m}Tc]-BPs) for use in bone scintigraphy to detect osteoporosis and other skeletal-related events (SREs), including bone metastases (1). These chemicals are known to promote osteoclast apoptosis and have a strong affinity for hydroxyapatite, a component of the bone matrix. The exact mechanism of action of these bone-seeking compounds is described in detail elsewhere (2-4). Although these labeled compounds have a high sensitivity, selectivity, and accuracy for the detection of SREs, they are known to generate some false positive and false negative results in the clinic (5). [^{18}F]-Fluoride is another nuclide that is commonly used for bone imaging with positron emission tomography (PET) and is believed to be superior to [^{99m}Tc]-BPs for the diagnosis of SREs (6); however, the main limitations of using ^{18}F are the high cost of production and the requirement of a cyclotron to produce it (5). In an effort to develop an imaging compound that does not have the limitations of tracers currently used to detect SREs with scintigraphy or PET, Suzuki et al. developed a bisphosphonate labeled with ^{68}Ga, which has been shown to be potentially useful for the PET imaging of the skeletal system (5).

The main advantage of using ^{68}Ga (half-life = 68 min; β^+ = 89%; E+β_{max} = 1.9 MeV) for bone imaging over either ^{99m}Tc (half-life = 6 h; γ^+ = 100%; E+γ_{max} = 140 keV) or ^{18}F (half-life = ~110 min; β^+ = 97%; E+β_{max} = 0.635 MeV) as a radiolabel is that ^{68}Ga can be produced economically on-site with a ^{68}Ge/^{68}Ga generator (5). Suzuki et al. coupled a BP with 1,4,7-triazacyclononane-1,4-7-triacetic acid (NOTA-BP) and labeled the product with ^{68}Ga to obtain [^{68}Ga]-NOTA-BP (5). The investigators then compared the biodistribution of [^{68}Ga]-NOTA-BP with that of [^{99m}Tc]-methylene diphosphonate ([^{99m}Tc]-MDP) and [^{18}F]fluoride in rats. [^{68}Ga]-NOTA-BP was also evaluated for the imaging of osteolytic bone metastasis in mice.

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Related Resource Links

Related chapters in MICAD

Protein and mRNA sequence of human farnesyl diphosphate synthase

Gene information regarding human farnesyl diphosphate synthase (GeneID: 2224)

Farnesyl diphosphate synthase in Online Mendelian Inheritance in Man (OMIM) database

Structure of farnesyl diphosphate synthase complexed with a bisphosphonate

Farnesyl diphosphate synthase in Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathways

Clinical trials with bisphosphonates (or diphosphonates)

Synthesis

[PubMed]

The synthesis of NOTA-BP and its labeling with ^{68}Ga have been described by Suzuki et al. (5). The radiochemical purity (RCP) of the labeled product was >95% as determined with radio thin-layer chromatography (RTLC; R_f = 0.3–0.4). The radiochemical yield (RCY) and specific activity of the final labeled product were not reported.

[^{99m}Tc]-MDP and ^{18}F were obtained from commercial or academic sources, but the RCP, RCY, and specific activity of these labeled products were not mentioned (5).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Using a hydroxyapatite (HA) binding assay, the B_{max} and K_d of [^{68}Ga]-NOTA-BP, [^{99m}Tc]-MDP, and ^{14}C-pamadronic acid were determined to be 14.37 nmol/mg and 0.0937 μM, 53.98 nmol/mg and 0.4898 μM, and 53.88 nmol/mg and 0.3066 μM, respectively (5). This indicated that [^{68}Ga]-NOTA-BP had a higher affinity for HA than either [^{99m}Tc]-MDP or ^{14}C-pamadronic acid, but [^{68}Ga]-NOTA-BP had a lower B_{max} than the latter two labeled compounds.

[^{68}Ga]-NOTA-BP was reported to maintain a radiochemical purity of 95% (as determined with RTLC) when incubated with rat plasma for up to 3 h at 37°C (5).

The distribution of different concentrations (10 nM, 1.0 μM, and 3.7 μM) of [^{68}Ga]-NOTA-BP, [^{99m}Tc]-MDP, and [^{18}F]fluoride in the blood cells of rats after a 30 min incubation at 37^{o} C was investigated by Suzuki et al. (5). The proportion of [^{68}Ga]-NOTA-BP in the blood cells was 6.5%–8.4%, which was comparable to that of [^{99m}Tc]-

MDP (7.1%–10.2%) but significantly lower ($P < 0.05$) than that of [^{18}F]fluoride (29.1%–29.7%).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{68}Ga]-NOTA-BP ($n = 6$ animals), [^{99m}Tc]-MDP ($n = 7$ animals), and ^{18}F ($n = 4$ animals) was studied in normal Wistar rats as described by Suzuki et al. (5). Each rat was intravenously injected with 1.0–4.0 MBq (27–104 μCi) of the labeled compound, and the rodents were euthanized 2 h after administration to determine the amount of radioactivity accumulated in the various tissues, including the bone (tibia and fibula). Data obtained from the study were presented as percent of injected dose per gram tissue (% ID/g). The amount of radioactivity in the blood from [^{68}Ga]-NOTA-BP, [^{99m}Tc]-MDP, and ^{18}F was 0.004 ± 0.0005% ID/g, 0.02 ± 0.005 ($P < 0.05$), and 0.01 ± 0.001% ID/g, respectively ($P < 0.05$), indicating that ^{18}F was cleared rapidly from circulation compared to the other two tracers. In the muscle, the accumulation of label from [^{68}Ga]-NOTA-BP, [^{99m}Tc]-MDP, and ^{18}F was 0.002 ± 0.0001% ID/g, 0.006 ± 0.0008% ID/g ($P < 0.05$), and 0.004 ± 0.0004% ID/g ($P < 0.05$), respectively, indicating that the accumulation of tracer from [^{68}Ga]-NOTA-BP in the muscle was significantly lower than that from either [^{99m}Tc]-MDP or ^{18}F. The accumulation of radioactivity from [^{68}Ga]-NOTA-BP, [^{99m}Tc]-MDP, and ^{18}F in the bone was 0.47 ± 0.21% ID/g, 0.41 ± 0.21% ID/g ($P < 0.05$), and 0.69 ± 0.22% ID/g ($P < 0.05$), respectively, showing that the uptake of ^{18}F by the bone was significantly higher than that of either [^{68}Ga]-NOTA-BP or [^{99m}Tc]-MDP. The bone/muscle uptake (B/M) ratios for [^{68}Ga]-NOTA-BP, [^{99m}Tc]-MDP, and ^{18}F were 2,048 ± 107, 747 ± 107 ($P < 0.05$), and 1,798 ± 206, respectively, showing that the B/M ratio of [^{68}Ga]-NOTA-BP was superior to that of [^{99m}Tc]-MDP and ^{18}F.

Using severe combined immunodeficient mice with osteolytic bone metastasis ($n = 3$ mice), the imaging potential of [^{68}Ga]-NOTA-BP was compared with that of [^{99m}Tc]-MDP (5). Each animal was injected with 6.04–8.36 MBq (163–225 μCi) [^{68}Ga]-NOTA-BP, and microPET images were acquired from the mice (under anesthesia) 1 h later. One day later, the same animals were injected with 18.0–19.5 MBq (489–526 μCi) [^{99m}Tc]-MDP, and gamma micro-single photon emission computed tomography (SPECT) planar images were obtained from the mice (under anesthesia) at 3.0–3.25 h after injection. A high accumulation of both tracers was observed at the osteolytic lesion on the right tibia of the animals; however, microPET images obtained with [^{68}Ga]-NOTA-BP showed a higher resolution than the micro-SPECT planar images acquired with [^{99m}Tc]-MDP.

From these studies, the investigators concluded that [^{68}Ga]-NOTA-BP can be used for the detection of osseous metastasis in mice, but further work is necessary before this agent can be used for the imaging of such lesions in humans (5).

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

1. Lin J., Luo S., Chen C., Qiu L., Wang Y., Cheng W., Ye W., Xia Y. *Preparation and preclinical pharmacological study on a novel bone imaging agent (99m)Tc-EMIDP.* Appl Radiat Isot. 2010;68(9):1616–22. PubMed PMID: 20363146.
2. Kimmel D.B. *Mechanism of action, pharmacokinetic and pharmacodynamic profile, and clinical applications of nitrogen-containing bisphosphonates.* J Dent Res. 2007;86(11): 1022–33. PubMed PMID: 17959891.
3. Zhang Y., Cao R., Yin F., Hudock M.P., Guo R.T., Krysiak K., Mukherjee S., Gao Y.G., Robinson H., Song Y., No J.H., Bergan K., Leon A., Cass L., Goddard A., Chang T.K., Lin F.Y., Van Beek E., Papapoulos S., Wang A.H., Kubo T., Ochi M., Mukkamala D., Oldfield E. *Lipophilic bisphosphonates as dual farnesyl/geranylgeranyl diphosphate synthase inhibitors: an X-ray and NMR investigation.* J Am Chem Soc. 2009;131(14): 5153–62. PubMed PMID: 19309137.
4. Mitterhauser M., Toegel S. *Radiopharmaceutical considerations on bone seeker uptake: should we learn from therapeutical targets of bisphosphonates?* Nucl Med Biol. 2011;38(5):617–8. PubMed PMID: 21718935.
5. Suzuki K., Satake M., Suwada J., Oshikiri S., Ashino H., Dozono H., Hino A., Kasahara H., Minamizawa T. *Synthesis and evaluation of a novel 68Ga-chelate-conjugated bisphosphonate as a bone-seeking agent for PET imaging.* Nucl Med Biol. 2011;38(7): 1011–8. PubMed PMID: 21982572.
6. Kruger S., Buck A.K., Mottaghy F.M., Hasenkamp E., Pauls S., Schumann C., Wibmer T., Merk T., Hombach V., Reske S.N. *Detection of bone metastases in patients with lung*

cancer: 99mTc-MDP planar bone scintigraphy, 18F-fluoride PET or 18F-FDG PET/CT. Eur J Nucl Med Mol Imaging. 2009;36(11):1807–12. PubMed PMID: 19504092.