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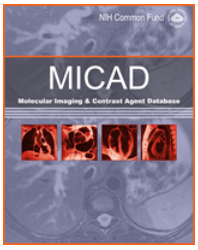


# $^{99m}$Tc-Labeled 5-amino-1,3-bis(ethylamine-(*N*,*N*-dimethyl diphosphonic acid)acetamido)benzene

## [$^{99m}$Tc]IPTMP

Puja Panwar, PhD,[1] Sweta Singh, M.Sc.,[2] Nitin Kumar, M.Sc.,[3] Harish Rawat, B.Sc.,[4] Anil Kumar Mishra, PhD,[5] and Arvind Chopra, PhD[6]

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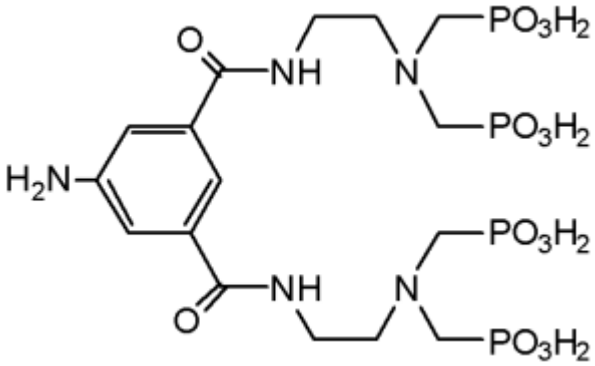
|---|---|
| **Chemical name:** | $^{99m}$Tc-Labeled 5-amino-1,3-bis(ethylamine-(*N*,*N*-dimethyl diphosphonic acid)acetamido)benzene |
| **Abbreviated name:** | [$^{99m}$Tc]IPTMP |
| **Synonym:** | 5-aminoisophthalate tetramethylene phosphonic acid (IPTMP) |
| **Agent Category:** | Compound |
| **Target:** | Farnesyl diphosphate synthase |
| **Target Category:** | Enzyme |
| **Method of detection:** | Single-photon emission computed tomography (SPECT); gamma planar imaging |
| **Source of signal / contrast:** | $^{99m}$Tc |
| **Activation:** | No |
| **Studies:** | • *In vitro*<br>• Rodents<br>• Non-primate non-rodent mammals |




Structure of IPTMP.

**Author Affiliations:** 1 Div. Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, New Delhi, 110054, India; Email: puja@inmas.drdo.in. 2 Div. Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, New Delhi, 110054, India; Email: kchuttani@yahoo.com. 3 Div. Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, New Delhi, 110054, India. 4 Div. Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, New Delhi, 110054, India. 5 Div. Cyclotron and Radiopharmaceutical Sciences, Institute of Nuclear Medicine and Allied Sciences, New Delhi, 110054, India; Email: akmishra@inmas.org. 6 National Center for Biotechnology Information, NLM, NIH, Bethesda, MD 20892; Email: micad@ncbi.nlm.nih.gov.

# Background

[PubMed]

Cancers such as those of the breast, prostate, kidney, and thyroid have a high incidence of metastases, particularly in the bone, which results in bone resorption, pain, hypercalcemia, spinal compression, decreased mobility, and even fractures (1). In addition, osteoporosis (bone resorption), a common condition experienced most frequently by menopausal women as well as aging women and men, often leads to bone fractures in these individuals (2). Although chemo- and radiotherapy are often used to treat bone metastases, none of these treatments control the progression of this disease or result in a better prognosis for the patient. Bisphosponates (BPs) or their nitrogen-containing derivatives (N-BPs) are the most commonly used compounds for the selective targeting and treatment of bone-related ailments observed during cancer metastases or osteoporosis (3, 4) because of their attraction to hydroxyapatite, a major component of bone, and because they alleviate, to some extent, the symptoms and complications arising from these conditions. The chemical structure, characteristics, and pharmacological behavior of BPs has been described by Hirabayashi and Fujisaki (3). Briefly, the parent BP compound contains a characteristic phosphate-carbon-phosphate (P-C-P) bond that is resistant to enzymatic digestion and has no substitution at the central carbon (5); N-BPs, however, have a nitrogen-containing moiety substituted on the carbon atom (6). BPs and N-BPs were shown to inhibit bone-related events by different mechanisms (7), and N-BPs were reported to be 100- to 10,000-fold more potent than BPs (8). BPs and N-BPs are approved by the United States Food and Drug Administration for the treatment of bone diseases such as osteoporosis, Paget's disease of the bone, hypercalcemia, and bone metastases. In addition, these drugs also being evaluated in clinical trials for the treatment and imaging of different bone-related disorders.

Accurate and early noninvasive detection of osteoporosis or bone metastases can assist in the development of a suitable treatment strategy and possibly improve the prognosis for a patient. Radiolabeled BPs, such as methyl diphosphonate (MDP) (9), hydroxymethylene diphosphonate, 1-hydroxyethylene diphosphonate, etc., are often used as imaging agents for the detection of bone remodeling (e.g., during cancer metastases) or repair (e.g., after a fracture) because these compounds tend to accumulate in osteoclasts at active bone sites (10). Although radiolabeled N-BPs have been used for the therapy of bone cancer in animal models (11) and humans (12), no N-BPs have been used for bone imaging. Panwar et al. (13) synthesized a $^{99m}$Tc-labeled multidentated N-BP, 5-amino-1,3-bis(ethylamine-(*N,N*-dimethyl phosphonic acid)acetamido)benzene (or 5-aminoisophthalate tetramethylene phosphonic acid ($^{99m}$Tc-IPTMP)) and investigated its biodistribution in mice. The accumulation of $^{99m}$Tc-IPTMP in select organs of the animals was compared to that of the same organs obtained from animals treated with $^{99m}$Tc-MDP. Whole-body scintigraphic imaging of rabbits treated with the radiolabeled compound was also performed by the investigators.

## Other sources of information

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)

Structure of farnesyl diphosphate synthase complexed with a bisphosphonate

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

Related chapters in MICAD

# Synthesis

[PubMed]

The chemical synthesis of IPTMP was described in detail by Panwar et al. (13). The final yield of the tetraphosphonate compound was reported to be 89% with a purity of >97%.

The labeling of IPTMP with $^{99m}$Tc was done in the presence of tin at a pH between 6.0 and 6.5 in 0.5 M sodium bicarbonate for 30 min at room temperature (13). The yield of $^{99m}$Tc-IPTMP was reported to be >97% with a radiochemical purity of >97% as determined with instant thin-layer paper chromatography–silica gel (ITLC-SC). The Rf of $^{99m}$Tc-IPTMP on ITLC-SC was 0.3, which indicates that only one species of the labeled compound was formed during the labeling process. The specific activity of the radiochemical was not reported.

The synthesis and specific activity of $^{99m}$Tc-MDP used for some studies were not reported (13).

The transchelation of $^{99m}$Tc from labeled MDP and IPTMP was investigated in the presence of 25–100 mM diethylenetriamine-pentaacetic acid (DTPA) (13). The transchelation of $^{99m}$Tc from labeled MDP increased with the concentration of DTPA to a maximum of 45%, but for $^{99m}$Tc-IPTMP the transchelation was reported to be 6% at all concentrations of DTPA.

# *In Vitro* Studies: Testing in Cells and Tissues

[PubMed]

$^{99m}$Tc-IPTMP was reported to be stable in human serum for up to 24 h under *in vitro* physiological conditions, similar to $^{99m}$Tc-MDP, and no transchelation of serum proteins was observed as determined by ITLC-SC (13).

# Animal Studies

## Rodents

[PubMed]

Panwar et al. investigated the biodistribution of $^{99m}$Tc-IPTMP in normal BALB/c mice (13). The mice ($n$ = 5 mice/time point) were injected with the radiolabeled compound intravenously through the tail vein and euthanized at predetermined time points starting at 30 min for up to 24 h after treatment. The major organs from the euthanized animals were removed, and accumulated radioactivity in the various organs was determined (presented as percent injected dose/gram tissue ± standard deviation (% ID/g ± SD)). Maximum uptake of radioactivity was observed in the bones, varying from 4.69 ± 0.92% ID/g at 30 min to 7.3 ± 0.69% ID/g at 4 h and 2.96 ± 0.06% ID/g at 24 h. The kidneys also showed a high uptake of the label (varying from 2.32 ± 0.01% ID/g at 30 min to 2.47 ± 0.07% ID/g at 4 h and 0.14 ± 0.12% ID/g at 24 h). Other organs showed an uptake varying from 0.12 ± 0.01% ID/g (stomach) to 0.64 ± 0.01% ID/g (blood) at 30 min and to 0.04 ± 0.05% ID/g (blood and liver) to 0.13 ± 0.03% ID/g (spleen) at 24 h after injection of the radiochemical.

The uptake of $^{99m}$Tc-MDP and $^{99m}$Tc-IPTMP by select organs (blood, kidneys, and bones) of the animals ($n$ = 5 mice/time point) was also determined (13). The uptake of $^{99m}$Tc-IPTMP by the bones was higher (6.6 ± 0.46% ID/g at 1 h and 7.3 ± 0.69% ID/g at 4 h) than that of $^{99m}$Tc-MDP (4.92 ± 0.15% ID/g at 1 h and 5.92 ± 0.36% ID/g at 4 h). A similar trend was noticed for the kidneys. The blood circulation of $^{99m}$Tc-IPTMP at 1 h after injection was higher (0.71 ± 0.08% ID/g) than that of $^{99m}$Tc-MDP (0.21 ± 0.01% ID/g). Both labeled compounds had a similar radioactivity profile in the blood at 4 h (0.20 ± 0.04% ID/g). These results suggest that $^{99m}$Tc-IPTMP has a higher affinity than $^{99m}$Tc-MDP for the bone tissue.

## Other Non-Primate Mammals

[PubMed]

For comparison purposes, scintigraphic imaging was performed on normal rabbits injected with either $^{99m}$Tc-IPTMP or $^{99m}$Tc-MDP (13). A comparable quality of images was obtained with the two radiolabeled compounds at 1 h ($^{99m}$Tc-IPTMP) and 3 h ($^{99m}$Tc-MDP) after treatment. It was evident that the radioactivity from both compounds accumulated primarily in the bones of the animals. This suggested that the uptake of $^{99m}$Tc-IPTMP by the bones was more rapid than that of $^{99m}$Tc-MDP. However, at 3 h the residual radioactivity in the skeleton of the rabbits was similar to both labeled compounds. Also, compared to $^{99m}$Tc-MDP, a higher accumulation of $^{99m}$Tc-IPTMP in the kidneys was observed both at 1 h and 3 h after treatment. These results reflected the same profile observed for radiolabel uptake by mice during the biodistribution investigation as described above (13).

With results obtained from the various studies, the investigators concluded that $^{99m}$Tc-IPTMP was rapidly incorporated into the skeletal tissue of mice and rabbits (13). The labeled compound was suitable for scintigraphic imaging of the skeleton in animals, but more work is required to develop it as a bone imaging agent for humans.

## Non-Human Primates

[PubMed]

No references are currently available.

# Human Studies

[PubMed]

No references are currently available.

# Supplemental Information

[Disclaimer]

No information is currently available.

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