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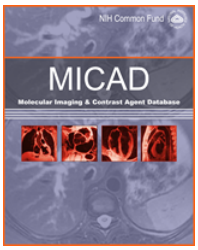


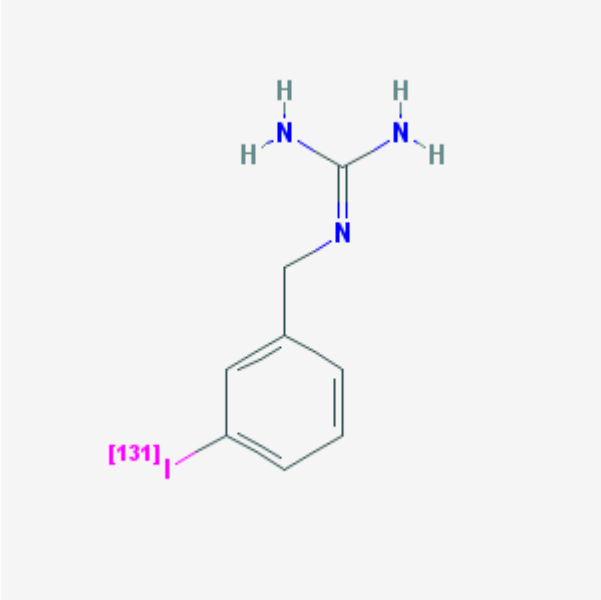
Meta-[radioiodinated]iodobenzylguanidine

[^{123}I/^{125}I/^{131}I]MIBG

The MICAD Research Team

Created: May 3, 2007; Updated: July 3, 2007.

Chemical name:	Meta-[radioiodinated]iodobenzylguanidine
Abbreviated name:	[^{123}I/^{125}I/^{131}I]MIBG
Synonym:	*m*-[^{123}I/^{125}I/^{131}I]MIBG; 2-[(3-iodophenyl)methyl]guanidine; Ultratrace™iobenguane ^{131}I; MyoMIBG-^{123}I injection; Pheo®MIBG-^{131}I injection
Agent Category:	Compound
Target:	Norepinephrine receptor
Target Category:	Receptor binding
Method of detection:	SPECT and planer gamma imaging
Source of signal:	^{123}I/^{125}I/^{131}I
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

Meta-iodobenzylguanidine (MIBG) is a norepinephrine (NE) analog that contains a benzyl and a guanidine group. Because it structurally resembles NE, neuroendocrine cells take up MIBG through an active mechanism and store it in the neurosecretory granules. This leads to specific concentration of the molecule in the neuroendocrine cells. MIBG radiolabeled with iodine (as ^{123}I, ^{125}I, or ^{131}I) is used for scintigraphy or therapy

of a variety of tumors that have an endocrine origin (1, 2). In addition, ^{123}I-labeled MIBG ([^{123}I]MIBG) is used for sympathetic innervation scintigraphy of the heart (3), and [^{125}I]MIBG is used to study adrenergic nerve changes during physiological stress, disease, or after the treatment of heart function (4). Among the iodine radiolabeled homologs of MIBG, [^{123}I]MIBG and [^{131}I]MIBG are used most often for diagnosis. In general, [^{123}I]MIBG is the clinical agent of choice because of its low effective dose and high-quality single-photon emission computed tomography (SPECT) results for cardiac sympathetic nerves, pheochromocytomas, and neuroendocrine tumors (2, 5).

Although [^{131}I]MIBG is approved by the United States Food and Drug Administration as an investigational new drug for clinical use (6, 7), [^{123}I]MIBG is not (2, 5). [^{131}I]MIBG is currently undergoing evaluation in phase 1 and phase 1/2 clinical trials in the United States for the treatment of neuroendocrine tumors. [^{123}I]MIBG is commercially available in Europe and both [^{123}I]MIBG and [^{131}I]MIBG are available as diagnostic radiopharmaceuticals in Japan. Guidelines for the use of [^{123}I/^{131}I]MIBG for tumor imaging are available from the European Association of Nuclear Medicine website.

Synthesis

[PubMed]

The synthesis of [^{123}I/^{125}I/^{131}I]MIBG was described by Wieland et al. in a US patent (8). The radiolabeled compounds were generated by radioiodide exchange with the appropriate iodine radioisotope using sodium iodide. In this chapter, only the synthesis of [^{123}I]MIBG is described. The other two radioisotopes ([^{125}I/^{131}I]MIBG) were synthesized using the same procedure, which provided a similar radiochemical yield and purity.

To start, m-iodobenzylamine was mixed with cyanamide and stirred with heating at 100°C for 4 h to obtain a solid that was dissolved in water. To this, a solution of potassium bicarbonate was added dropwise with stirring and the precipitated meta-iodoguanidine bicarbonate was collected. The precipitate was washed with water and dried *in vacuo* with a yield of 85%. The bicarbonate salt was suspended in water and sulfuric acid was slowly added. The resulting suspension was warmed to a solution and the desired m-iodobenzylguanidine sulfate was crystallized when it cooled to room temperature. The crystals were washed with cold water and dried *in vacuo* with a yield of 78%. The sulfate was dissolved in water and refluxed at 140°C in an oil bath with Na[^{123}I] for 20–30 min, during which time the water was allowed to evaporate. More water was added while the temperature was maintained, and the water was again allowed to evaporate; this procedure was repeated several times for a total reaction time of 3 h to obtain a residue. The residue was redissolved in water and purified through a glass column packed with Cellex D anion exchange cellulose to remove any unreacted and radiolabeled iodide and iodate.

Purity of the product was determined by thin-layer chromatography to be >98%, and the absence of rearranged isomeric impurities was confirmed with high-performance liquid chromatography on a micro Bondapak C18 column. The radioiodinated product yield was 90–95% with a specific activity of 20.35–410.7 MBq/μmol (0.56–11.10 mCi/μmol) and a purity of >98%.

Methods for the synthesis of no-carrier-added (NCA) [^{123}I]MIBG and [^{131}I]MIBG are also available (9-11).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The differential toxicity of [^{123}I]MIBG in neuroblastoma (NB) cell lines (SK-N-SH and SK-N-BE(2)) and human cells of hematopoietic lineage (HL-60 and bone marrow stem cells) was investigated (12). [^{123}I]MIBG strongly inhibited proliferation of the NB cell lines but was sparing for cells of hematopoietic lineage. The

investigators also observed that meta-trimethylsilylbenzylguanidine (MTBG), one of the precursors used for the synthesis of NCA MIBG, was toxic towards the NB and Hl-60 cells. This indicated that NCA preparations of MIBG should be further purified before clinical use.

The use of either [^{125}I]MIBG or [^{131}I]MIBG, alone or in combination, to treat neuroblastoma multicellular tumor spheroids derived from the SK-N-SH cell line was investigated *in vitro* (13). The investigators concluded that [^{125}I]MIBG by itself was not superior to [^{131}I]MIBG for treatment; however, a combination of the two radiotracers was a more effective treatment than using [^{131}I]MIBG alone.

The uptake of [^{125}I]MIBG was determined in a pheochromocytoma cell line (PC-12) after exposure to 1-methyl-4-phenyl-1,2,3,6-terrahydroxypyridine (MPTP), a chemical used to induce Parkinson's disease in mice (14). The accumulation of [^{125}I]MIBG in the PC-12 cells was blocked almost completely by MPTP, which indicated that neurons were damaged by the exposure to MPTP.

The application of gene therapy with [^{131}I]MIBG was explored by Fullerton et al. in EJ138 cells, a bladder cancer cell line (15). The cells were transfected with a gene encoding the noradrenaline transporter under the control of tumor-specific promoters. The uptake of [^{131}I]MIBG was assessed in these cells. Radiolabel accumulation and cell death were observed to be dose-dependent. The investigators suggested the possible use of this strategy in the treatment of bladder cancer.

Anti-cancer drugs such as topotecan, cisplatin, and doxorubicin were shown to induce increased accumulation of [^{131}I]MIBG in NB cells (16, 17).

Animal Studies

Rodents

[PubMed]

The use of NCA and carrier-added [^{123}I]MIBG for the assessment of cardiac sympathetic nerve activity in rats was evaluated by SPECT scintigraphy (18). A higher cardiac uptake of the NCA than of the carrier-added radiolabel was observed, and the investigators concluded that the NCA variety could provide a better scintigraphic assessment of the myocardial sympathetic nervous system.

In a study designed to investigate the distribution of [^{125}I]MIBG in various organs of the rat, Wieland et al. showed that the radiotracer accumulated mainly in the heart, liver, and lungs of these animals (19). Among these organs, the heart had the highest accumulation of label. Other studies demonstrated that [^{125}I]MIBG could be used to investigate the *in vivo* functioning of rat adrenergic neurons (4) and modulation of the atrioventricular nodal and bundle (His bundle) sympathetic activity in the heart (20). Sisson et al (21). suggested that the movement of [^{125}I]MIBG may be used as an indication of neuronal injury and heart function in rats. This radiotracer was also used to demonstrate that the endocardial and epicardial layers of the left ventricle in the rat heart were probably innervated differently (22). Wakasugi et al (23, 24). demonstrated that [^{125}I]MIBG could be used to determine adriamycin cardiomyopathy in rats.

In a study with Syrian hamsters, a reduced accumulation of [^{125}I]MIBG in the heart during cardiomyopathy was shown to be caused by its release from neuronal junctions as a result of activation of the renin-angiotensin system (25).

Intraperitoneal pretreatment of mice bearing xenografts of human NB cell lines with cisplatin and doxorubicin showed an increased accumulation of [^{125}I]MIBG in the tumors (17), which indicated that the drugs selectively increase radiation doses delivered to neuroblastoma tumors.

Mice pretreated with MPTP can be used as an animal model for Parkinson's disease. Takatsu et al. (26) observed a significantly reduced cardiac accumulation of [^{125}I]MIBG in MPTP-treated animals and suggested that this agent or unknown toxic substrates in experimental or human Parkinson's disease may damage the postganglionic sympathetic nerves.

Other Non-Primate Mammals

[PubMed]

The *ex vivo* distribution of [^{125}I]MIBG was studied in different organs of the dog (19). Accumulation of the tracer was observed primarily in the heart, liver, and lungs, which is similar to observations in the rat. The dog heart was shown to take up the label rapidly and lose it gradually over 24 h. Pretreatment of dogs with reserpine resulted in a 30% decrease in [^{125}I]MIBG accumulation (19). Sisson et al (4). demonstrated that [^{125}I]MIBG could be used to measure acute changes in neuronal activity of the dog heart. The distribution of [^{125}I]MIBG was investigated in normal and denervated canine hearts (27). Normal hearts showed an uptake of MIBG at 5 min and after 3 hrs, but the denervated hearts showed an uptake only at the early time point. This indicated that the label accumulated mainly in the neuronal tissue and was quickly lost from the non-neuronal tissues.

Non-Human Primates

[PubMed]

The distribution of [^{125}I]MIBG has been studied in various organs of the monkey (19, 28). In these animals highest uptake was observed in the liver, followed by the heart and lungs. [^{125}I]MIBG was also used as a myocardial imaging agent in the monkeys.

Human Studies

[PubMed]

Kline et al. (29) demonstrated the use of [^{125}I]MIBG as a myocardial imaging agent in humans. The distribution of this tracer was studied in normal and transplanted human hearts (27). The investigators showed significant accumulation of radiolabel at 5 min and 3 hr in the normal heart; however, the transplanted organ showed no localization of the label either at 5 min or 3 hr, indicating that the non-neuronal uptake mechanism for this compound is not significant in humans. Regional sympathetic denervation of the heart was suggested to be the cause of the lack of radioactivity uptake by the transplanted organs. Sisson et al. (30) showed that [^{125}I]MIBG could be used to determine the regional distribution and functioning of the human adrenergic nervous system.

The uptake of [^{125}I]MIBG in neuroblastoma tumors in children was investigated by Moyes et al. (31). The investigators observed that quantitative uptake of the label varied between patients and even between different parts of the individual tumors. Also, the more differentiated tumors took up higher amounts of label compared to the undifferentiated tumors.

The use of [^{131}I]MIGB as an investigational new drug for the treatment of refractory NB and malignant pheochromocytomas (PHEO) or paragangliomas (PGL) is being evaluated (6, 7). The investigators reported that 67% of the patients with malignant PHEO or PGL who showed a good uptake of the radiolabeled compound had either complete remission, partial response, or stable disease (6). Because of its high response rate and low nonhematologic toxicity, the incorporation of [^{131}I]MIBG as an agent for a multi-modal therapy of NB was suggested (7).

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