^{99m}Tc-2-Methoxyisobutylisonitrile

^{99m}Tc-MIBI

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Chemical name:	^{99m}Tc-2-Methoxyisobutylisonitrile	
Abbreviated name:	^{99m}Tc-MIBI	
Synonym:	^{99m}Tc-hexakismethoxyisobutylisonitrile, ^{99m}Tc-Sestamibi	
Agent category:	Compound	
Target:	P-glycoprotein, MDR-1, mitochondria	
Target category:	Transporter	
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging	
Source of signal:	^{99m}Tc	
Activation:	No	
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans	No structure is available in PubChem.

Background

[PubMed]

Lipophilic cations are capable of passive diffusion into the cytoplasm and mitochondria of cells in response to a large negative plasma- and mitochondrial- membrane potentials. ^{99m}Tc-2-methoxyisobutylisonitrile (MIBI) was taken up into both normal and malignant cells being driven by metabolic demand and membrane potential (1) (2) ^{99m}Tc-MIBI was originally developed as a myocardial perfusion imaging agent and subsequently as tumor

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imaging agent. The uptake of ^{99m}Tc-MIBI is also used as a biomarker for cellular metabolism in malignant tumors.

One of the mechanisms of cells to escape the cytotoxic effects of chemotherapeutic agents, such as Adriamycin, Vinca alkaloids, epipodophyllotoxins, actinomycin D, and taxol, is to limit their presence inside the cells by a multidrug resistance (MDR-1) gene protein. The MDR-1 gene encodes a transmembrane P-glycoprotein (Pgp) as a multidrug transporter that is capable of actively pumping a variety of agents out of the cells (3). Overexpression of Pgp in tumor cells leads to resistance to anticancer drugs (4). MIBI is a transport substrate of Pgp in a variety of tumor cells (5). Another mechanism of tumor cells to escape anticancer treatments is to acquire a defective apoptotic program. Apoptosis is a highly regulated, multistep process involving the mitochondria. Bcl-2 is an integral protein on the outer mitochondrial membrane, nuclear membrane, and endoplasmic reticulum. Cancer cells have been found to have a high level of Bcl-2, which is anti-apoptotic. Overproduction of the Bcl-2 protein also prevents cell death induced by nearly all cytotoxic anticancer drugs and radiation (6, 7). MIBI is being used as a myocardial perfusion imaging agent in clinical use to assess the risk of future cardiac events. It is also used as a tumor-imaging agent in breast, lung, thyroid, and brain cancers.

Related Resource Links:

- Chapters in MICAD (P-glycoprotein)
- Gene information in NCBI (P-glycoprotein)
- Articles in OMIM (P-glycoprotein)
- Clinical trials (P-glycoprotein, ^{99m}Tc-MIBI)
- Drug information in FDA (^{99m}Tc-MIBI)

Synthesis

[PubMed]

^{99m}Tc-MIBI was prepared by reacting 2-methoxyisobutylisonitrile with ^{99m}Tc-O_4^- in the presence of sodium dithionite. Radiochemical purity was greater than 98% after Sep-Pak purification (8). A commercial lyophilized kit is available (9).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Cultured chick embryo heart cells, myocytes, accumulated [^{99m}Tc]MIBI with a half-time of 9.3 min reaching a plateau at 40 min. An apparent K_d of 7 x 10^{-5}M was assessed. The uptake could be inhibited by a metabolic inhibitor, iodoacetate, with an IC_{50} of 5 x 10^{-6}M (10). Subcellular analysis of ^{99m}Tc-MIBI in isolated rat hearts showed that about 90% of MIBI activity was associated with the mitochondria (11). A panel of eight human carcinoma cell lines and one leukemia cell line was incubated with ^{99m}Tc-MIBI for one hour. The uptakes were varied from 5-28% of the activity in the external media. In

contrast, normal Chinese hamster lung fibroblasts and human peripheral blood mononuclear leukocytes did not exhibit a uptake of more than 2% (12). The uptake was dependent on energy, plasma membrane potential and mitochondria membrane potential.

Animal studies

Rodent Studies

[PubMed]

Rats showed a good uptake in the heart, liver, kidneys, and intestine with low uptake in the lungs after 30-60 min of injection of [^{99m}Tc]MIBI (9, 13). Various tumor models in rodents were evaluated to determine the role of MDR and Bcl-2 in the uptake of [^{99m}Tc]MIBI by cancer cells [PubMed]. Myocardial perfusion studies were performed in mice and rats with [^{99m}Tc]MIBI to determine the actual infarct size [PubMed].

Other Non-Primate Mammal Studies

[PubMed]

Myocardial blood flow was found to be linearly related to ^{99m}Tc-MIBI uptake in dogs with minimal washout and redistribution (14). Excellent static myocardial images were obtained for several hours. Many myocardial perfusion and infraction experiments were performed in rabbits [PubMed], pigs [PubMed] and dogs [PubMed] using ^{99m}Tc-MIBI.

Non-Human Primate Studies

[PubMed]

Myocardial images with ^{99m}Tc-MIBI of the monkey showed good contrast and low wash-out (9). There was a rapid blood clearance and hepatic excretion.

Human Studies

[PubMed]

[^{99m}Tc]MIBI is used as an important myocardial perfusion imaging agent to evaluate coronary artery disease and myocardial infraction [PubMed]. [^{99m}Tc]MIBI is readily accumulated in the heart. Human dosimetry was estimated from 17 normal volunteers (15). The large and small intestines received the highest dose of radioactivity, followed by the gallbladder, urinary bladder, and kidneys. The total body absorbed dose was 4.4 mGy/GBq (16 mrad/mCi). Many clinical studies have been performed to correlate [^{99m}Tc]MIBI uptake or clearance with histological, molecular, and biochemical markers of various cellular processes, including apoptosis, proliferation, Pgp expression, and angiogenesis. The early tracer uptake reflects the mitochondrial status, which is affected by both apoptosis and proliferation. On the other hand, the tracer clearance reflects the

activity of drug transporters such as Pgp. The uptake and clearance of [^{99m}Tc]MIBI by cancer cells may determine tumor response to anticancer treatment as shown in breast cancer patients (16). In addition to tumor localization, [^{99m}Tc]MIBI has been used to predict and monitor sensitivity to anticancer treatments in breast cancer [PubMed], lung cancer [PubMed], thyroid cancer [PubMed], hepatocellular carcinoma [PubMed], lymphoma [PubMed], and gastric cancer (17).

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