[^{18}F]Fluoromisonidazole

[^{18}F]FMISO

The MICAD Research Team

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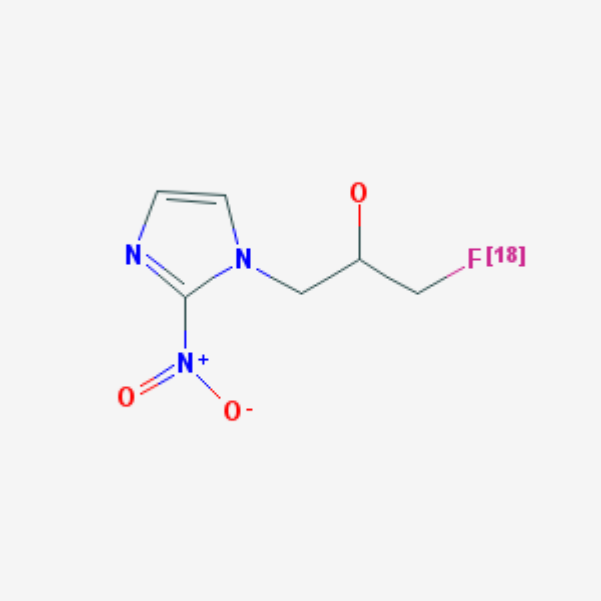
Chemical name:	1-(2-Nitro-imidazolyl)-3-[^{18}F]fluoro-2-propanol; 1*H*-1-(3-[^{18}F]fluoro-2-hydroxypropyl)-2-nitroimidazole
Abbreviated name:	[^{18}F]FMISO
Synonym:	[^{18}F]Fluoromisonidazole
Agent Category:	Compound
Target:	Hypoxic cells (macromolecules)
Target Category:	Intracellular reduction and binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Other non-primate mammals • Humans



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Background

[PubMed]

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Hypoxia in malignant tumors can affect the outcome of anti-cancer treatments. Malignant tumors are relatively resistant to chemotherapy and irradiative therapy because of their lack of oxygen, a potent radiosensitizer. This is the reason for the multitude of efforts to develop methods and imaging techniques for measuring oxygen in tissues. Radiolabeled 2-nitroimidazole compounds have been developed to specifically detect tumor hypoxia, offering a less invasive and less technically demanding alternative to the Eppendorf (oxygen) electrode method. The imaging technique also avoids sampling bias.

[^{18}F]Fluoromisonidazole ([^{18}F]FMISO) was proposed as a tracer for determining tumor hypoxia *in vivo* with clinical positron emission tomography (PET) in 1984. Since then, it has become the most widely used nitroimidazole derivate for this technique (1, 2). [^{18}F]FMISO has been shown to selectively bind to hypoxic cells both *in vitro* and *in vivo*. It is used to quantitatively assess tumor hypoxia in lung, brain, and head-and-neck cancer patients (3, 4) and in the hearts of patients with myocardial ischemia (5, 6).

[^{18}F]FMISO is reduced and binds selectively to macromolecules within hypoxic cells. [^{18}F]FMISO is relatively hydrophilic and diffuses across cell membranes, showing a passive distribution in normal tissues (4). Because of the slow reaction mechanisms and the absence of active transport of the tracer molecules, the identification and quantification of hypoxic tumor areas necessitate long examination protocols. Also, in severe conditions ($pO_2 \leq$ 2-3 mmHg), hypoxia is underestimated by [^{18}F]FMISO uptake measurements, possibly because of the existence of a threshold below which the bioreduction and cell uptake of [^{18}F]FMISO does not increase any further (7).

Synthesis

[PubMed]

Two main strategies for synthesizing [^{18}F]FMISO are reported in the literature: a nucleophilic substitution on a protected precursor (8, 9) or epoxide ring opening; and the production of the intermediate [^{18}F]epifluorohydrin, followed by coupling to 2-nitroimidazole (10). Grierson et al. (11) proposed a two-step synthesis producing [^{18}F]FMISO with a high yield (40% end of bombardment (EOB)), high purity (>99%), and a specific activity of 37 TBq/mmol. Through this method, the fluoroalkylating agent [^{18}F]epifluorohydrin is first obtained by displacing (2*R*)-(−)glycidyltosylate (GOTS). [^{18}F]FMISO is then obtained by reaction of [^{18}F]epifluorohydrin with 2-nitroimidazole and further purification through high-performance liquid chromatography (HPLC).

One of the most promising methods seems to be a nucleophilic substitution of the tolysate-leaving group by [^{18}F]fluoride on the tetrahydropyranyl-protected precursor 1-(2′-nitro-1′-imidazolyl)-2-*O*-tetrahydropyranyl-3-*O*-toluenesulfonylpropanediol (NITTP), with hydrolysis of the protecting group. An automated synthesis of [^{18}F]FMISO by this method has been reported in the literature, using either HPLC or Sep-Paks for the purification of the radiotracer (1, 8). The chemical yield obtained when using NITTP was found to be ≤40% (and reproducible), with a radiochemical purity ≥97%, and a specific activity of about 34 TBq/mmol (8).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

[^{18}F]FMISO uptake was reported in various studies using tumor cell lines such as V-79, EMT-6, RIF-1, and canine osteosarcoma, incubated under hypoxic conditions (7). Those experiments showed *in vitro* good selectivity of [^{18}F]FMISO for hypoxic cells. Reported uptake ratios between hypoxic and normoxic cultures ranged from 12 to 27, depending on the tumor type. In other *in vitro* studies using V-79, EMT-6(UW), RIF-1, and CaOs-1 cell lines, it was shown that the decreased uptake in hypoxic cells was directly related to increased oxygen concentrations, and that an O_2 level between 720 and 2300 ppm reduced [^{18}F]FMISO binding by 50%, relative to binding under anoxic conditions (12). Studies using Chinese hamster V79-171b spheroids exposed to 50 mM [^{3}H]FMISO for 1 to 6 h under aerobic (5% CO_2 in air), hypoxic (5% CO_2, 5% O_2, in N_2), or anoxic (5% CO_2 in N_2) conditions showed that the uptake in anoxic spheroids was similar to that in anoxic cell monolayers. In experiments performed by Casciari et al. (13), [^{18}F]FMISO-PET showed a tumor hypoxic fraction of 15%, a value consistent with those obtained from radiation survival assays (17%) and measurements of oxygen consumption (22%).

Rodents

[PubMed]

Rodent studies aimed at evaluating tumor hypoxia have been performed using [^{18}F]FMISO-PET and by comparing the obtained results with those from immunohistochemical (IHC) staining techniques. In studies on WAG/Rij rats bearing transplanted syngeneic rhabdomyosarcoma (R1) tumors, a statistically significant correlation ($P < 0.05$) was obtained between the hypoxic volumes defined with [^{18}F]FMISO-PET and the volumes derived from the pimonidazole-stained tumor sections ($r = 0.9066$; $P = 0.0001$), regardless of the selected threshold between 1.4 and 2.2. A heterogeneous distribution of hypoxia was observed both with histology and [^{18}F]FMISO autoradiography (2). Biodistribution studies by Rasey et al. (14) showed that 36% and 57% of [^{18}F]FMISO-derived activity was metabolized at 2 and 4 h after injection, respectively.

Rodent studies such as the one by Rasey et al. (15) on 36B10 rat gliomas determined the radiobiologically hypoxic fraction from radiation response data using the paired cell survival curve technique (method 1) in comparison with mathematical modeling of time-activity data (method 2) acquired by [^{18}F]FMISO-PET uptake. The radiobiologically hypoxic fraction determined for tumors in air-breathing rats during imaging was 6.1% (95% CL, 4.3-8.6%). A comparable value was obtained by modeling [^{18}F]FMISO time-activity data (7. 4%; 95% CL, 2.5-17.3%). In contrast, the two methods led to different values for rats breathing 10% oxygen. In that case, the hypoxic fraction determined by the first method was 13.1% (95% CL, 7.9-8.3%), 43% lower than the value obtained by

method 2. The authors suggested that such a discrepancy might be attributable in large part to the inability of [^{18}F]FMISO to identify hypoxic cells at $pO_2 \leq$ 2-3 mm Hg.

Non-Human Primates

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

Several pig and dog studies aimed at quantifying the relationship between [^{18}F]FMISO uptake and the hypoxic fraction in tumors were reported in the literature. Piert et al.(16) found a negative exponential relationship between liver standardized uptake values (SUVs) and the oxygen pressure in the liver of domestic pigs. They determined the activity of [^{18}F]FMISO in relation to the hepatic oxygen availability and the partial pressure of oxygen in tissue (tPO_2) to define a critical oxygen delivery on a regional basis. The experimental procedure involved injecting [^{18}F]FMISO into pigs 2 h after onset of regional liver hypoxia caused by the occlusion of the branches of the hepatic artery. The fractional concentration of inspired oxygen (FiO_2) was set to 0.67 in a first group of animals and to 0.21 in a second group. The SUV for [^{18}F]FMISO was calculated from tissue samples obtained 3 h after the injection of [^{18}F]FMISO (about 10 MBq/kg body weight) and compared with the regional total hepatic oxygen delivery (DO_2) calculated from the regional arterial and portal venous flow and the oxygen content of the arterial and portal venous blood. Results showed a significant decrease of DO_2 in occluded liver tissue samples (first group: 0.063 (0.044-0.089); second group: 0.046 (0.032-0.066)) compared with normal flow segments (first group: 0.177 (0.124-0.252); second group: 0.179 (0.128-0.25) ml x min(-1) x g(-1); geometric mean (95% confidence limits): $P < 0.01$ in the first group and $P < 0.001$ in the second group). The tPO_2 of occluded segments (first group: 5.1 (3.2-8.1); second group: 3.9 (2.4-6.2) mm Hg) showed a substantial decrease compared with normal flow segments (first group: 20.2 (12.6-32.5); second group: 22.4 (14.3-35.2) mm Hg; $P < 0.01$ in first group and $P < 0.001$ in second group (17)).

Comparative studies of [^{18}F]FMISO and [^{18}F]fluorodeoxyglucose (FDG) on dogs with viable myocardium were reported in the literature (18). *Ex vivo* analysis of both ischemic and normal heart tissue showed that FMISO uptake was consistently greater than FDG uptake, and that when analyzed relative to endocardial-epicardial location, endocardial FMISO uptake was significantly greater in all hypoperfused samples.

Human Studies

[PubMed]

[^{18}F]FMISO has been used in humans to assess hypoxia and perfusion in brain tumors. Data obtained by Bruehlmeier et al. (4) using [^{18}F]FMISO-PET and [^{15}O]H_2O on patients with glioblastoma showed a positive correlation between [^{18}F]FMISO tumor uptake at 0-5 min after injection and [^{15}O]H_2O, with *r* values between 0.42 and 0.86. No relation between [^{18}F]FMISO uptake and perfusion was found at 150-170 after injection. Despite the nature of the covalent binding of [^{18}F]FMISO metabolites (19), a degree of reversibility of [^{18}F]FMISO tumor binding was reported by Bruehlmeier et al., who suggested this might be attributable to a limited "back diffusing" effect from the cells.

[^{18}F]FMISO-PET human studies, including comparative studies using both [^{18}F]FMISO and FDG (20), showed that [^{18}F]FMISO uptake varied greatly, depending on the tumor types and the tumor sites in the same patient (21, 22). Generally, increased [^{18}F]FMISO tumor uptake was found in tumor margins rather than in the centers (4).

[^{18}F]FMISO-PET has also been used as a noninvasive method to assess tumor hypoxia in humans with head-and-neck cancer (HNC) and non-small cell lung cancer (NSCLC). In a reported study (3) involving 40 patients with advanced HNC (n = 26) or NSCLC (n = 14) before curative radiotherapy, dynamic (0-15 min) and static PET scans were performed over a 4-h time period after injection. SUVs and ratios-to-reference tissues (mediastinum or muscle) were calculated. Results for HNC showed that patients with local recurrence could be separated from disease-free patients by SUV, 4 h after injection (SUV > 2 for all recurrences). On the other hand, for NSCLC, no similar correlation was observed. The tumor-to-muscle ratios (T/Mu) and tumor-to-mediastinum ratios (T/Me) at 4 h after injection correlated with the risk of relapse in both tumor entities: all patients with a T/Me > 2.0 (NSCLC, n = 5) or with a T/Mu > 1.6 (HNC, n = 5) had tumor recurrence, whereas only 3 of the remaining 11 patients experienced a recurrence (27%).

A variety of compartment models using human [^{18}F]FMISO-PET data have been proposed to quantify tumor hypoxia. In 2005, Thorwarth et al. (23) developed a model based on dynamic HNC patient data. This model takes into account the variations of tumor vasculature obtained by immunohistochemical studies and the slow uptake of severely hypoxic and necrotic tissues overlooked by previous models based on SUVs (24).

References

1. Tang G., Wang M., Tang X., Gan M., Luo L. Fully automated one-pot synthesis of [(18)F]fluoromisonidazole. Nucl Med Biol. 2005;32(5):553–8. PubMed PMID: 15982586.
2. Dubois L., Landuyt W., Haustermans K., Dupont P., Bormans G., Vermaelen P., Flamen P., Verbeken E., Mortelmans L. Evaluation of hypoxia in an experimental rat tumour model by [(18)F]fluoromisonidazole PET and immunohistochemistry. Br J Cancer. 2004;91(11):1947–54. PubMed PMID: 15520822.
3. Eschmann S.M., Paulsen F., Reimold M., Dittmann H., Welz S., Reischl G., Machulla H.J., Bares R. Prognostic impact of hypoxia imaging with 18F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy. J Nucl Med. 2005;46(2):253–60. PubMed PMID: 15695784.

4. Bruehlmeier M., Roelcke U., Schubiger P.A., Ametamey S.M. Assessment of hypoxia and perfusion in human brain tumors using PET with 18F-fluoromisonidazole and 15O-H2O. J Nucl Med. 2004;45(11):1851–9. PubMed PMID: 15534054.
5. Markus R., Reutens D.C., Kazui S., Read S., Wright P., Pearce D.C., Tochon-Danguy H.J., Sachinidis J.I., Donnan G.A. Hypoxic tissue in ischaemic stroke: persistence and clinical consequences of spontaneous survival. Brain. 2004;127(Pt 6):1427–36. PubMed PMID: 15130953.
6. Guadagno J.V., Donnan G.A., Markus R., Gillard J.H., Baron J.C. Imaging the ischaemic penumbra. Curr Opin Neurol. 2004;17(1):61–7. PubMed PMID: 15090879.
7. Couturier O., Luxen A., Chatal J.F., Vuillez J.P., Rigo P., Hustinx R. Fluorinated tracers for imaging cancer with positron emission tomography. Eur J Nucl Med Mol Imaging. 2004;31(8):1182–206. PubMed PMID: 15241631.
8. Kamarainen E.L., Kyllonen T., Nihtila O., Bjork H., Solin O. Preparation of fluorine-18-labelled fluoromisonidazole using different synthesis methods. J Label Compd Radiopharm. 2004;47(1):37–45.
9. Patt M., Kuntzsch M., Machulla H.J. Preparation of [18F]fluoromisonidazole by nucleophilic substitution on THP-protected precursor: yield dependence on reaction parameters. J Radioanal Nucl Chem. 1999;240(3):925–27.
10. Jerabeck, P.A., T.B. Patrick, M.R. Kilbourn, D.D. Dischimo, and M.J. Welch, *Synthesis and biodistribution of 18F-labeled fluoronitroimidazoles: potential in vivo markers of hypoxic tissue.* Int J Radiat Appl Instrum [A], 1986(37): p. 599–605.
11. Grierson J.R., Link J.M., Mathis C.A., Rasey J.S., Krohn K.A. A radiosynthesis of fluorine-18 fluoromisonidazole. J Nucl Med. 1989;30(3):343–50. PubMed PMID: 2738663.
12. Rasey J.S., Nelson N.J., Chin L., Evans M.L., Grunbaum Z. Characteristics of the binding of labeled fluoromisonidazole in cells in vitro. Radiat Res. 1990;122(3):301–8. PubMed PMID: 2356284.
13. Casciari J.J., Rasey J.S. Determination of the radiobiologically hypoxic fraction in multicellular spheroids from data on the uptake of [3H]fluoromisonidazole. Radiat Res. 1995;141(1):28–36. PubMed PMID: 7997512.
14. Rasey J.S., Hofstrand P.D., Chin L.K., Tewson T.J. Characterization of [18F]fluoroetanidazole, a new radiopharmaceutical for detecting tumor hypoxia. J Nucl Med. 1999;40(6):1072–9. PubMed PMID: 10452326.
15. Rasey J.S., Casciari J.J., Hofstrand P.D., Muzi M., Graham M.M., Chin L.K. Determining hypoxic fraction in a rat glioma by uptake of radiolabeled fluoromisonidazole. Radiat Res. 2000;153(1):84–92. PubMed PMID: 10630981.
16. Piert M., Machulla H., Becker G., Stahlschmidt A., Patt M., Aldinger P., Dissmann P.D., Fischer H., Bares R., Becker H.D., Lauchart W. Introducing fluorine-18 fluoromisonidazole positron emission tomography for the localisation and quantification of pig liver hypoxia. Eur J Nucl Med. 1999;26(2):95–109. PubMed PMID: 9933343.
17. Piert M., Machulla H.J., Becker G., Aldinger P., Winter E., Bares R. Dependency of the [18F]fluoromisonidazole uptake on oxygen delivery and tissue oxygenation in the porcine liver. Nucl Med Biol. 2000;27(8):693–700. PubMed PMID: 11150699.

18. Caldwell J.H., Revenaugh J.R., Martin G.V., Johnson P.M., Rasey J.S., Krohn K.A. Comparison of fluorine-18-fluorodeoxyglucose and tritiated fluoromisonidazole uptake during low-flow ischemia. J Nucl Med. 1995;36(9):1633–8. PubMed PMID: 7658224.
19. Casciari J.J., Graham M.M., Rasey J.S. A modeling approach for quantifying tumor hypoxia with [F-18]fluoromisonidazole PET time-activity data. Med Phys. 1995;22(7):1127–39. PubMed PMID: 7565388.
20. Gagel B., Reinartz P., Dimartino E., Zimny M., Pinkawa M., Maneschi P., Stanzel S., Hamacher K., Coenen H.H., Westhofen M., Bull U., Eble M.J. pO(2) Polarography versus positron emission tomography ([(18)F] fluoromisonidazole, [(18)F]-2-fluoro-2'-deoxyglucose). An appraisal of radiotherapeutically relevant hypoxia. Strahlenther Onkol. 2004;180(10):616–22. PubMed PMID: 15480509.
21. Rasey J.S., Koh W.J., Evans M.L., Peterson L.M., Lewellen T.K., Graham M.M., Krohn K.A. Quantifying regional hypoxia in human tumors with positron emission tomography of [18F]fluoromisonidazole: a pretherapy study of 37 patients. Int J Radiat Oncol Biol Phys. 1996;36(2):417–28. PubMed PMID: 8892467.
22. Rajendran J.G., Wilson D.C., Conrad E.U., Peterson L.M., Bruckner J.D., Rasey J.S., Chin L.K., Hofstrand P.D., Grierson J.R., Eary J.F., Krohn K.A. [(18)F]FMISO and [(18)F]FDG PET imaging in soft tissue sarcomas: correlation of hypoxia, metabolism and VEGF expression. Eur J Nucl Med Mol Imaging. 2003;30(5):695–704. PubMed PMID: 12632200.
23. Janssen H.L., Hoebers F.J., Sprong D., Goethals L., Williams K.J., Stratford I.J., Haustermans K.M., Balm A.J., Begg A.C. Differentiation-associated staining with anti-pimonidazole antibodies in head and neck tumors. Radiother Oncol. 2004;70(1): 91–7. PubMed PMID: 15036858.
24. Thorwarth D., Eschmann S.M., Paulsen F., Alber M. A kinetic model for dynamic [18F]-Fmiso PET data to analyse tumour hypoxia. Phys Med Biol. 2005;50(10):2209–24. PubMed PMID: 15876662.