[^{18}F]Fluoroerythronitroimidazole

[^{18}F]FETNIM

The MICAD Research Team

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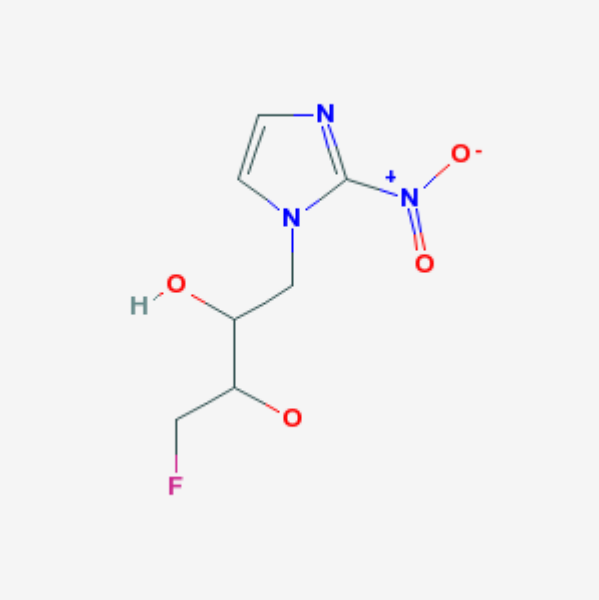
Chemical name:	4-[^{18}F]Fluoro-2,3-dihydroxy-1(2'-nitro-1'imidazolyl)butane
Abbreviated name:	[^{18}F]FETNIM
Synonym:	[^{18}F]Fluoroerythronitroimidazole
Agent Category:	Compound
Target:	Hypoxic cells (macromolecules)
Target Category:	Intracellular reduction and binding
Method of detection:	PET
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Other non-primate mammals • Humans



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Background

[PubMed]

Hypoxia in malignant tumors can be a major factor limiting the efficacy of radiotherapy and may also be a predictive factor for the occurrence of metastatic disease. This is the reason for a multitude of efforts to develop methods and imaging techniques for measuring oxygen in tissues. Methods for measuring tumor hypoxia use diverse

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technologies including biological, chemical and physical methods. Nitroimidazoles, used in conjunction with positron emission tomographic imaging (PET), offer a less invasive and less technically demanding alternative to the Eppendorf (oxygen) electrode method.

Nitroimidazoles are reduced intracellularly in cells. In aerobic cells, the reduced nitroimidazole is immediately reoxidised and washed out rapidly. On the other hand, an environment of low oxygen concentration induces further reductive reactions that ultimately lead to the formation of either reactive products that are able to covalently bind to cell components, or charged species that diffuse slowly out of the tissues (1). The bioreductive metabolism of 2-nitroimidazoles leads to nitroso (2e-), hydroxylamine (4e-), and amine (6e-) derivatives. When the fragmentation of the imidazole ring occurs, reactive portions of the molecule, such as glyoxal, bind to macromolecular components of cells in tissues and tumors (2)

Initial development of nitroimidazoles for *in vivo* imaging used radiohalogenated derivatives of misonidazole, some of which have been used in patients. Fluoromisonidazole ([^{18}F]FMISO) is the most widely used nitroimidazole derivate for imaging hypoxia using PET. The two main problematic issues with [^{18}F]FMISO are: i) its relatively low concentration within the lesion, ii) the need to wait several hours to allow clearance of the agent from the normoxic background tissue (contrast between lesion and background is typically < 2:1 at about 90 min after injection). Even with PET, this combination of circumstances can make successful evaluation of hypoxic lesions a challenge.

[^{18}F]Fluoroerythronitroimidazole ([^{18}F]FETNIM) is a novel imaging agent currently under investigation for the *in vivo* detection of tumor hypoxia using PET. [^{18}F]FETNIM is more hydrophilic than [^{18}F]FMISO, and therefore can be eliminated more rapidly from well-oxygenated tissues, allowing a higher tumor-to-background ratio. Preliminary research has shown that [^{18}F]FETNIM has a slow peripheral metabolism, little defluorination, and trapping in hypoxic tumor tissue. But despite encouraging results, further studies need to be performed to justify the development of [^{18}F]FETNIM-PET on a larger scale as a non-invasive assessment method for tumor hypoxia.

Synthesis

[PubMed]

The synthesis of [^{18}F]FETNIM was first described by Yang et al. (3) in 1995. In the reported method, [^{18}F]FETNIM is synthesized from the precursor 1-(2'-nitro-1'-imidazolyl)-2,3-*O*-isopropylidene-4-tosyloxybutane by nucleophilic displacement of the tosyloxy group with [^{18}F]Fluoride followed by acidic hydrolysis of the diol-protecting group.

A slightly modified method proposed in 2001 by Grönroos et al. (4) consists of the following steps: After producing [^{18}F]Fluoride by bombarding ^{18}O-enriched water using a cyclotron, the target water is removed by azeotropic distillation with acetronitrile under

reduced pressure, the tosylate is dissolved in dry acetonitrile and [^{18}F]Fluoride/Kryptofix 222/K^+ complex and heated for 8 min at 90 °C. Hydrochloric acid (2mol/L) is then added to the dry residue, and a hydrolysis performed at 90 °C for 2 min. After cooling, 2N NaOH is added and the mixture is then filtered and injected onto a HPLC column. After elution with a saline solution containing 2% ethanol (pH adjusted at 4.7), the fraction containing [^{18}F]FETNIM is eluted for 13 min. and collected.

The entire synthetic procedure can be completed in 50 min. The radiochemical purity obtained is ≥ 95%, the radiochemical yields (corrected for decay) range between 13 and 20%, with an associated specific activity of c.a. 330 GBq/µmol.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication currently available

Animal Studies

Rodents

[PubMed]

Biodistribution studies of [^{18}F]FETNIM were performed on 20 female Sprague-Dawley rats bearing multiple mammary tumors (4). Two sets of studies were performed: a first one using [^{18}F]FETNIM injected doses of 8.5 ± 2.2MBq (0.23 ± 0.06mCi) for data recorded at 15, 30 and 60 min after intravenous injection of the radiotracer; the second one using [^{18}F]FETNIM injected doses of 50 ± 10 MBq (1.35 ± 0.27 mCi) for data recorded at 120 and 240 min. The highest tumor-to-blood radioactivity ratio was observed at 120min (1.79 ± 0.64 SD); it remained constant thereafter until 240 min. The organ showing the highest uptake at 120 min was the kidney (0.397 ± 0.092% ID/g tissue), while the lowest uptake was observed in the cerebellum (0.063 ± 0.009%ID/g). The bone uptake measured by Grönroos et al. (4) (0.058 ± 0.007% ID/g tissue) showed only a minimal defluorination. On the other hand, a high uptake in the bone marrow (0.37 ± 0.07% ID/g tissue) was observed at 1h post-injection.

[^{18}F]FETNIM showed a much lower liver uptake (1.68 ± 0.62 liver-to-blood ratio) than reported by Rasey et al. for [^{18}F]FMISO-PET (5). One should keep in mind though, that direct comparisons are often difficult to establish and to rely on, when studies are performed using different imaging protocols or methods of analysis.

Chung et al. (6) evaluated the tumor uptake of both [^{18}F]Flurorodeoxyglucose ([^{18}F]FDG) and [^{18}F]FETNIM in male ICR mice bearing sarcoma 180 cell line xenografts. Radiotracers were injected intravenously (185 kBq); the tumors used in the experiments weighed 0.26 - 5.82 g. For both radiotracers, the tumor uptake (per-gram radiotracer) was inversely proportional to the tumor weight, but also depended on the distribution of necrosis. The tumor uptake values reported for [^{18}F]FETNIM and

[^{18}F]FDG were 1.77 ± 0.48% ID/g and 6.27 ± 2.53% ID/g, respectively. [^{18}F]FETNIM showed a closer correlation ($r = -0.593$, $p < 0.05$) than [^{18}F]FDG ($r = -0.447$, $p < 0.05$) and was found to accumulate in both viable and partially necrotic areas. ([^{18}F]FDG accumulated in viable areas only).

Non-Human Primates

[PubMed]

No publication is currently available.

Other Non-Primate Mammals

[PubMed]

Very limited investigations on non-primate mammals have been performed so far. [^{18}F]FETNIM-PET studies by Grönroos et al. (4) on rats and dogs (using radio-TLC analyses) showed that the amount of unchanged [^{18}F]FETNIM in dog venous plasma remained constant at 86% ± 4% over a 90 min dynamic scan, and that the binding of [^{18}F]FETNIM was minimal. The reported average amount of unbound [^{18}F]FETNIM in dogs was 95% ± 5% (for a 5-90 min period of time post-injection.

Human Studies

[PubMed]

Human studies using [^{18}F]FETNIM-PET have been performed on head-and-neck cancer (HNC) patients. Those investigations have largely been carried out by researchers at the University of Turku, Finland (7-9). For those studies, a dynamic PET imaging was used in combination with measurements of blood flow using [^{15}O]H_2O (median dose:1,152 MBq (31.1 mCi); dose range: 1,014 -1,800 MBq (27.4 - 48.6 mCi)) and blood volume using [^{15}O]CO (median dose: 2,699 MBq (72.9 mCi); dose range: 2,496 - 2,992 MBq (67.4 - 80.8 mCi)). In one reported study using eight untreated HNC patients (7), the tumor blood flow observed was 5 to 30 times greater than in muscle, in contrast to blood volume which remained identical in the two tissues. The tumor distribution volume (calculated using the graphic analysis applied by Logan et al. (10), except for the early phase of [^{18}F]FETNIM peak activity) correlated strongly with the standardized uptake value (SUV) of [^{18}F]FETNIM between 60 and 120 min, and with blood flow. The highest correlation was obtained at 90 min ($r^2 = 0.935$; $P < 0.0001$).

In a study by Tolvanen et al. (9) using intravenous injections of [^{18}F]FETNIM on HNC patients (mean activity 366 MBq), the reported effective dose to a 70-kg adult was 0.015 or 0.019 mSv/MBq, for a 2- and 4-h voiding intervals. The critical organ with the highest absorbed dose was the urinary bladder wall (0.062 and 0.127 mGy/MBq for a 2-h and 4-h intervals). Absorbed doses in all other organs were at least five times smaller than the bladder wall dose (e.g. 0.006 and 0.014 mGy/MBq for the brain and gallbladder wall respectively, at 2-h and 4-h intervals. With an injected activity of 370 MBq (100mCi), the

radiation doses were found generally comparable to those of other related radionuclide imaging procedures.

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