2-[(2-chloro-2′-^{18}F-fluorodiethyl)amino]-2H-1,3,2-oxazaphosphorinane-2-oxide

^{18}F-F-CP

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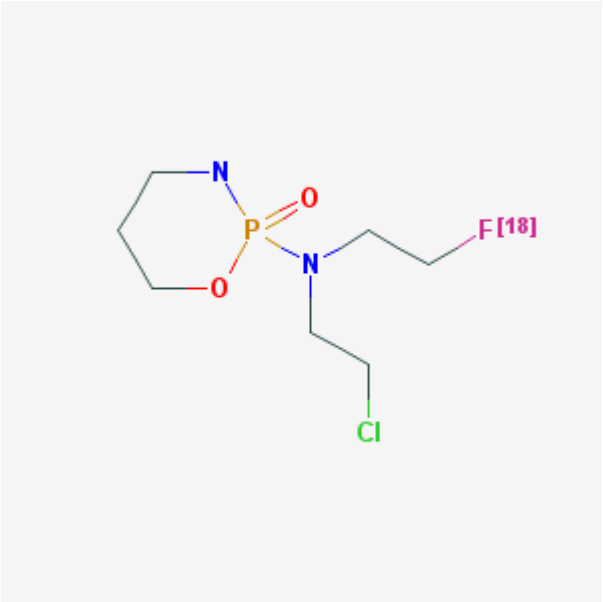
Chemical name:	2-[(2-chloro-2'-^{18}F-fluorodiethyl)amino]-2H-1,3,2-oxazaphosphorinane-2-oxide
Abbreviated name:	^{18}F-F-CP
Synonym:	^{18}F-Fluorocyclophosphamide; Cytoxan®, Neosar®
Agent Category:	Compound
Target:	DNA
Target Category:	Alkylation
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	Yes (by cytochrome p450 enzymes)
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

2-[(2-Chloro-2'-^{18}F-fluorodiethyl)amino]-2H-1,3,2-oxazaphosphorinane-2-oxide (also known as fluorocyclophosphamide and abbreviated as CP) is widely used for the treatment of cancers, as an immunosuppressant in systemic rheumatic diseases, and also as an agent to mobilize stem cells during autologous stem cell transplantation and multiple sclerosis (1-4). Actually, CP is a pro-drug that must be activated by hepatic cytochrome P450 enzymes before it can generate the DNA-alkylating phosphoramide mustard and other cellular toxic species that are known to mediate its effects (5). The biotransformation pathway of CP has been described elsewhere (6, 7). Individual differences in the metabolism, including biodistribution and pharmacokinetics, of CP and its analogs are known to influence the final outcome of clinical therapy (8). Therefore, it would be helpful to know before initiating therapy with CP or its analogs whether a patient will benefit from the treatment. Also, cell lines are known to rapidly develop resistance to CP activity, and prior exposure of the cells to other alkylating agents elevates the chances of developing the CP-resistant phenotype (9, 10). Two aldehyde dehydrogenases (ALDH1A1 and ALDH3A1) and glutathione S-transferase are known to detoxify CP and its metabolites and are involved in the development of resistance to this drug (9, 11).

Lacan et al. envisioned that knowledge regarding the biodistribution and metabolism of CP in a patient would help healthcare providers devise a suitable chemotherapeutic regimen and perhaps predict clinical outcome of the therapy for an individual (12). The investigators synthesized a radioactive fluorine (^{18}F)-labeled analog of CP, ^{18}F-fluorocyclophosphamide (^{18}F-F-CP), to study the *in vivo* metabolism of CP in tumors. Instead of using the multi-step procedure available for the synthesis of the analog to generate the compound, they applied a direct halogenation exchange protocol with a commercially available precursor (12, 13). The biodistribution of ^{18}F-F-CP was studied in mice bearing xenograft tumors (14).

CP is approved by the United States Food and Drug Administration for the treatment of a variety of cancers and is currently being evaluated in several clinical trials.

Synthesis

[PubMed]

The synthesis of ^{18}F-F-CP was described in detail by Lacan et al. (12). Briefly, modified procedures were used to produce 2-[(2-chloro-2'-fluorodiethyl)amino]-2H-1,3,2-oxazaphosphorinane-2-oxide (12). A halogen exchange reaction was performed with this compound to obtain ^{18}F-F-CP. To do this, ^{18}F-fluorine exchange was carried out in the presence of $^{18}F^{-}$, potassium bicarbonate, and acetonitrile with Kryptofix 222 at 110°C for 10 min. The total synthesis time was 60–75 min, and the labeling yield at the end of bombardment was 1.1–4.9% (from 16 batches). The radiochemical purity of ^{18}F-F-CP was

determined by high-performance liquid chromatography to be >99%, and the specific activity was 54–960 Ci/mmol (1.45–25.94 BGq/mmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* cytotoxicity of ^{18}F-F-CP was compared to that of CP with MCF-7 cells (of human breast cancer origin) using a cell proliferation assay (14). The drug was activated with human liver microsomes as described by the investigators. The cells were subsequently exposed to different concentrations of the activated drugs for 24 h and assayed for cell proliferation. Cytotoxicity of the activated drugs was also compared to that of the pro-drugs. Both CP and ^{18}F-F-CP were observed to be significantly more toxic to the cells after activation compared to the non-activated versions ($P < 0.01$). The investigators observed that a nearly 20-fold higher concentration of the non-activated drug was required to achieve the same effect as the metabolically activated compounds (14).

Animal Studies

Rodents

[PubMed]

The biodistribution of ^{18}F-F-CP was investigated in nude mice bearing MCF-7 cell xenograft tumors (14). Mice ($n = 8$) were injected intraperitoneally with the labeled CP, and the animals were euthanized after 1 h. The biodistribution of ^{18}F-F-CP was also investigated in another group of mice ($n = 8$) injected with different concentrations of unlabeled CP before treatment with the labeled compound. The visceral organs and blood were collected from each animal of the two respective groups, and they were weighed and counted for incorporation of radioactivity. The uptake after injecting ^{18}F-F-CP into the animals was also assessed by positron emission tomography (PET) imaging.

The uptake of ^{18}F-F-CP, after injection into the animals, was observed primarily in those organs that were related to the metabolism and excretion of the drug (14). Highest uptake of the label was observed in the kidneys and followed by the liver; the lowest uptake was observed in the brain, and intermediate levels were detected in the tumors. The tumor/tissue and tumor/blood ratios of the labeled drug were not reported. The investigators reported that biodistribution of the labeled drug as observed by PET imaging correlated well with the activity detected in the various harvested organs. They also observed that administration of ~700-fold excess of cold CP did not change the distribution kinetics of the labeled drug in the animals. In addition, the degree of ^{18}F-F-CP uptake by the tumor was observed to predict the degree of subsequent response to CP administration to the animal.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

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