[^{123}I]Iomazenil

[^{123}I]IMZ

The MICAD Research Team

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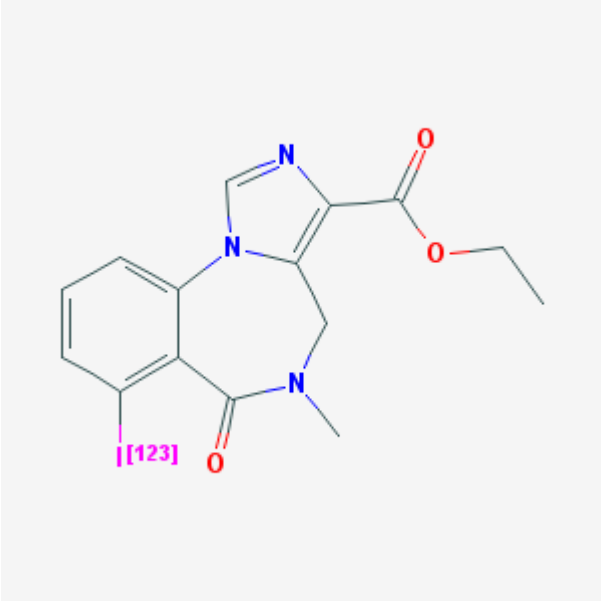
Chemical name:	[^{123}I]Iomazenil
Abbreviated name:	[^{123}I]IMZ
Synonym:	
Agent Category:	Compound
Target:	Central-type benzodiazepine receptors (on neurons)
Target Category:	Ligand binding
Method of detection:	SPECT
Source of signal:	^{123}I
Activation:	No
Studies:	• *In vitro* • Rodents • Other non-primate mammals • Non-human primates • Humans



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Background

[PubMed]

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[^{123}I]Iomazenil ([^{123}I]IMZ) is a ligand displaying high affinity for central-type benzodiazepine receptors, with high brain uptake and little nonspecific binding. It is a useful marker of neuronal viability. [^{123}I]IMZ has been successfully used as a probe for single photon emission computed tomography (SPECT) in numerous clinical studies of diseases such Alzheimer's [PubMed], epilepsy [PubMed], or cerebral ischemia [PubMed], for which alterations of benzodiazepine receptors have been reported (1, 2).

Synthesis

[PubMed]

[^{123}I]IMZ is readily available commercially. Details on its synthesis, however, are scarcely reported in the research literature. A possible preparation method is given by Eersels et al. (3), who recommend using a nucleophilic exchange rather than an electrophilic route because of the conjugation of the carbonyl group in iomazenil.

The reported method involves flushing (with N_2) and heating (at 121°C for 25 min) a reaction mixture kit consisting of 1 mg of bromo-mazenil, 0.2 mg of $SnSO_4$, 4 mg of 2,5-dihydroxybenzoic acid, and 5 mg of citric acid together with ^{123}I (37MBq; 1mCi). The labeling yield obtained is between 80% and 90%. Additional purification of the radiochemical can be done by high-performance liquid chromatography (HPLC) separation, dilution with an isotonic citrate buffer (pH 4), filtration, and sterilization. This additional procedure increases the purity of [^{123}I]IMZ to more than 97%, with an overall yield of 70-80%.

A comparison of the destannylation approach to the original ^{123}I for the bromo-substitution route can be found in the article by Zea-Ponce et al. (4).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The biodistribution, metabolism, and excretion of [^{123}I]IMZ have been studied in rats, rabbits, and humans. Studies showed that in all of the species, [^{123}I]IMZ was rapidly metabolized, and more than 90% of the administrated radioactivity was excreted within the first 24 h. For rats and humans, the dominant metabolites were found to be the acid metabolite (R-COOH), the glucuronide of the acid (R-COOH-Glc), and the free iodide (I-). In rabbits, R-COOH, the oxidative metabolite (R'-CH2COOH), and I- were found. On the basis of these findings, Yoshimura et al. (5) suggested that possible metabolic pathways of [^{123}I]IMZ were hydrolysis, oxidation, conjugation, and de-iodination. Experimental data also showed that the metabolites of [^{123}I]IMZ did not cross the blood-brain barrier.

Several studies aimed at determining the binding potential (defined as the ratio the receptor density and the binding affinity) of [^{123}I]IMZ, using kinetic and equilibrium methods, can be found in the literature (6, 7). Using 12 postmortem samples of human

brain, Abi-Dargham et al. (8) found that the SPECT *in vitro* measurements derived from the rate constants were consistent with SPECT *in vivo* measurements (9, 10). Simulation studies performed by Onishi et al. (11) using SPECT and blood data from six healthy volunteers and five patients suggested that, in the normal brain, the scan time at which a single SPECT image best represented the relative receptor binding was 3.0-3.5 h after injection. This finding was supported by data from the volunteers taking part in the study.

Binding potential values can also be obtained by reference tissue methods, using either one or several tissue compartment models (6). Nevertheless, such methods have limitations, in particular with low receptor densities. They generally yield lower values than conventional kinetic modeling using an arterial input function.

Animal Studies

Rodents

[PubMed]

Research using rat models showed that [^{123}I]IMZ was a useful marker of neuronal viability. In a study by Kaji et al. (12), neuronal DNA was still intact in the ischemic regions where [^{123}I]IMZ accumulation was preserved, and [^{123}I]IMZ had the potential to significantly detect the region with DNA scission as a reduction in lesion/normal ratios. Kuge et al. (13) showed that in rats with the cerebral artery occluded intraluminally, [^{123}I]IMZ uptake markedly decreased in the infarct regions at 4 and 24 h after the insult.

Using [^{125}I]IMZ, Morimoto et al. (14) investigated regional changes in central-type benzodiazepine receptors in the cortical dysplasia model of epilepsy in rats. In this study, pregnant rats were irradiated at day 17 of gestation with 1.2 Gy to produce cortical dysplasia in their pups. *In vitro* autoradiography with [^{125}I]IMZ performed at 8 weeks after birth showed that [^{125}I]IMZ binding was significantly decreased in various cortical regions of the *in utero* irradiated rats, including the bilateral frontal cortex (down to 92-93% of control); cingulate cortex (91-92%); hippocampal areas CA1 (95%), CA2 (94-95%), and CA4 (95-96%); and caudate/putamen (90-94%).

Other Non-Primate Mammals

[PubMed]

To determine whether benzodiazepine receptor or regional cerebral blood flow (rCBF) imaging was more sensitive in the detection of epileptic foci, Kurokawa et al. (15) examined simultaneously the benzodiazepine receptor and rCBF distribution changes in hippocampal kindled rabbits with *in vivo* double tracer autoradiography using [^{125}I]IMZ and ^{99m}Tc-labeled hexamethylpropylene amine oxime (^{99m}Tc-HMPAO). Visual and quantitative analyses showed that benzodiazepine receptor imaging was much more sensitive in the detection of epileptic foci than rCBF imaging and, therefore, more useful in clinical epilepsy.

Non-Human Primates

[PubMed]

SPECT imaging with [^{123}I]IMZ was shown to be a valuable means of quantifying central neuroreceptor density and affinity in baboons. Studies by Laruelle et al. (16, 17), who measured arterial and brain regional activities in three baboons after a single bolus injection of the benzodiazepine antagonist [^{123}I]IMZ, showed the feasibility of quantitative measurement of benzodiazepine receptors by kinetic analysis of SPECT data and the inadequacy of empirical methods of analysis, such as counts ratios, to evaluate differences in receptor density.

In a study by Sybirska et al. (18), SPECT imaging with [^{123}I]IMZ was also used to measure benzodiazepine neuroreceptor occupancy of the agonist lorazepam administered at supratherapeutic doses in monkeys. In this study, the effects of doses of lorazepam (cumulative dose, 0.5 mg/kg) higher than the therapeutic doses (0.03 mg/kg, i.v.) were examined in a stepwise displacement paradigm. Results strongly suggested that single, therapeutically relevant doses of lorazepam occupy a relatively small percentage (i.e., <3%) of benzodiazepine receptors, and that benzodiazepine binding sites have a significant (i.e., >97%) receptor reserve.

Zoghbi et al. (19) performed pharmacokinetics studies of [^{123}I]IMZ in two hypothermic and three normothermic anesthetized monkeys and compared the results to those obtained with five healthy human volunteers. Data showed that, after intravenous injection, [^{123}I]IMZ rapidly diffused outside the vascular bed and was cleared from the arterial plasma tri-exponentially, and that it was metabolized mainly to a polar radiometabolite in the human, whereas an additional lipophilic radiometabolite was detected in the monkey. Organ analysis from a monkey given [^{123}I]IMZ showed that the parent compound was actively taken up by peripheral organs. The polar radiometabolite accumulated mainly in the bile and the kidneys, whereas the non-polar radiometabolite accumulated in the urine and kidneys.

Human Studies

[PubMed]

Human studies have shown the potential of [^{123}I]IMZ for evaluating the neuronal viability (or damage) after an ischemic stroke (12). One example is the study by Moriwaki et al. (20) performed on 15 patients with angiographically confirmed, unilateral, severe occlusive lesions (occlusion or >70% stenosis) in the carotid system. Dong et al. (21) compared [^{123}I]IMZ SPECT images with the cerebral blood flow, cerebral metabolic rate of oxygen ($CMRO_2$), and cerebral metabolic rate of glucose (CMRGlc) by positron emission tomography in the chronic stage of ischemic stroke. They also showed that [^{123}I]IMZ could assess neuronal damage after an ischemic insult to the brain.

SPECT studies by Dey et al. (22) on human brains showed a strong uptake of [^{123}I]IMZ in a distribution consistent with benzodiazepine receptor binding (22). In this study, serial total body scans were obtained in healthy volunteers after thyroid blockade. Abdominal imaging showed significant activity retention within the urinary and gastrointestinal tracts consistent with excretion via these routes. The absorbed dose to the urinary bladder was calculated to be 0.19 mGy/MBq; to the lower large intestine, 0.079 mGy/MBq; to the upper large intestine, 0.066 mGy/MBq; and to the thyroid, 0.063 mGy/MBq.

Verhoeff et al. (23) calculated the absorbed radiation doses of [^{123}I]IMZ in various human organs using whole-body scans, blood samples, and urine from seven adult humans and applied the MIRD method. The urinary bladder wall (0.15 mGy/MBq), lower large intestinal wall (0.071 mGy/MBq), testes (0.044 mGy/MBq), and upper large intestinal wall (0.038 mGy/MBq) received the highest absorbed doses. The average effective dose equivalent of [^{123}I]IMZ was estimated to be 0.033 mSv/MBq..

Ito et al. (24) developed a simple, autoradiographic method for the quantification of benzodiazepine by using one SPECT scan and calibrated the standard input function with one blood sampling.

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