N^1,N^1-diethyl-N^4-(7-[^{125}I]iodoquinolin-4-yl)pentane-1,4-diamine

^{125}I IQ

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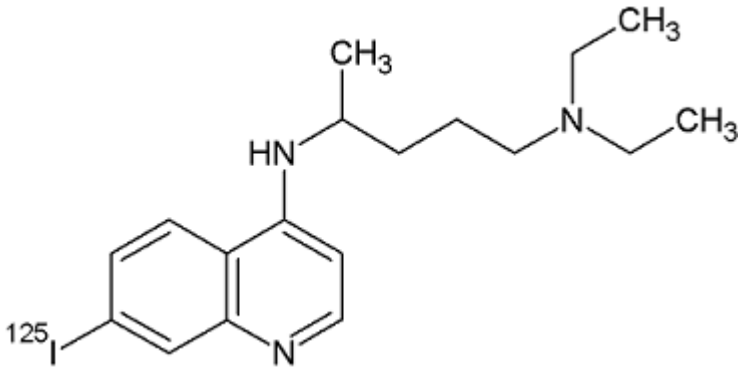
Chemical name:	N^1,N^1-diethyl-N^4-(7-[^{125}I]iodoquinolin-4-yl)pentane-1,4-diamine
Abbreviated name:	^{125}I IQ
Synonym:	IQ, iodoquine
Agent Category:	Compounds
Target:	Aldehyde dehydrogenase 1A1 (ALDH1)
Target Category:	Enzyme
Method of detection:	Single-photon emission computed tomography (SPECT) and planar imaging
Source of signal / contrast:	^{125}I
Activation:	No
Studies:	• *In vitro* • Rodents



Structure of ^{125}I IQ

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Background

[PubMed]

N^1,N^1-diethyl-N^4-(7-[^{125}I]iodoquinolin-4-yl)pentane-1,4-diamine, abbreviated as ^{125}I IQ, is a compound synthesized by Chin et al. for imaging cancer stem cells (CSCs) by targeting aldehyde dehydrogenase 1A1 (ALDH1) (1).

CSCs, also known as tumor-initiating cells, have been defined as a minor population of quiescent cells that possess the capacity for self-renewal, can generate heterogeneous lineages of cancer cells, and are resistant to conventional treatment (2, 3). Currently, there are two conflicting models proposed for cancer development: the "stochastic model," which proposes that all cells have an equal possibility of acquiring mutations and initiating a tumor; and the "hierarchy model," which proposes that only a distinct and small subset of cancer cells serve as CSCs and give rise to tumors (2, 4). The latter is becoming more popular in the field of tumor biology, and the focus of treatment is shifting from cytotoxic therapy that indiscriminately kills tumor cells to CSC-targeted therapy (5). A key issue to establish CSC-targeted imaging and therapy is the identification of biomarkers that can be used to identify and isolate CSCs from diverse cell populations (1, 3).

The cytosolic activity of the enzyme ALDH1 has been shown to be a reliable marker for CSCs in various types of solid tumors (6, 7). Evidence shows that tumor cells with highly expressed ALDH1 are highly tumorigenic, and the high activity of ALDH1 is associated with poor prognosis of many types of tumors. Growing evidence further suggests that ALDH1 is not only a putative stem cell marker but may actually play multiple roles that contribute to stem cell self-protection, differentiation, and self-renewal (4). Chin et al. tested the feasibility of iodoquine (IQ) to localize CSCs by targeting the high ALDH1 activity in tumors (1). IQ is structurally identical to chloroquine (6) with the exception of the halogen substitution of iodine for chlorine. CQ is known as a weak base anti-malarial drug, which accumulates within the digestive vacuoles of parasites as well as within the lysosomes of tumor cells (8). CQ is simply metabolized by the hepatic cytochrome P450 to *N*-desethylchloroquine and then excreted from kidneys. Recently, Graves et al. used proteomics techniques to determine that ALDH1 is a selective target for CQ (9, 10). These characteristics make CQ an attractive candidate for high-contrast tumor imaging. Chin et al. hypothesized that the structural similarity of IQ to CQ could confer the biochemical behavior and properties similar to the CQ (1). The studies by Chin et al. supported the hypothesis and suggested that IQ is a potential radiotracer for identifying CSCs with high ALDH1 expression (1).

Related Resource Links:

Nucleotides and proteins of aldehyde dehydrogenases

Bioassays of aldehyde dehydrogenase 1A1 in PubChem

Structures and relevant information of chloroquine and derivatives in PubChem

Synthesis

[PubMed]

Chin et al. first synthesized the unlabeled IQ in a single step from the commercially available 4-chloro-7-iodoquinoline in 65% yield (1). The tin precursor was then synthesized *via* the Stille reaction of unlabeled IQ with excess hexabutylditin in 67% yield. The tin precursor was radioiodinated with ^{125}I, ^{131}I, and ^{123}I with no-carrier-added synthesis with average radiochemical yields of 59.5 ± 12.5% (n = 9), 58.2 ± 14.3% (n = 4), and 57.5 ± 14.8% (n = 9), respectively. The radiochemical purity was >99%. Lipophilicity measurements with an octanol-water system revealed a partition coefficient (log P) of 0.26 ± 0.04 for ^{125}I IQ, which is lower than the optimal value of 2.0–3.5 as recommended for passive brain entry (1). The specific activity was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Cell uptake of ^{125}I IQ was evaluated from 0.5 h to 4 h after incubation with cells from several cell lines (L1210cpa, L1210, A549, and MG456), and the results were expressed as a percent of the incubation dose (%) (1). L1210 cyclophosphamide-resistant (cpa) leukemia/lymphoma cell line (L1210cpa) constitutively expresses a high level of ALDH1, and its parental line L1210 expresses only a low level of ALDH1. A549 lung cancer and MG456 glioblastoma cell lines are two lines presenting high ALDH1 expression. The expression levels in these cell lines were confirmed with Western blot analysis. The results showed that L1210cpa cells had uptake levels of ^{125}I IQ significantly higher than the parental line L1210 at all time points ($P < 0.001$) (Table 1). However, blocking studies with cold IQ showed no significant difference for the cell uptake between L1210 and L1210cpa cell lines, suggesting a nonspecific uptake mechanism such as passive diffusion (data not shown). High uptake of ^{125}I IQ was also observed in A549 and CD133$^+$ MG456 cells at all time points (Table 1).

Table 1: Cell uptake of ^{125}I IQ at various time points after incubation with cells (%).

Cell line	ALDH1 expression	30 min	1 h	2 h	4 h
L1210 cpa	high	20.7 ± 1.4	21.3 ± 0.9	20.6 ± 0.7	15.7 ± 0.7
L1210	low	11.0 ± 0.5	11.0 ± 0.4	9.4 ± 0.3	7.5 ± 0.4
A549	high	41.5 ± 2.4	43.7 ± 2.6	51.8 ± 2.0	55.6 ± 2.8
CD133$^+$ MG456	high	81.5 ± 0.9	88.8 ± 0.4	87.8 ± 2.1	87.0 ± 2.4

*The ALDH1 expression level was based on the Western blotting results; no quantitative data described.

In a separate experiment, Chin et al. isolated the $CD133^+$ stem cell subfraction from MG456 mouse xenograft tumors and evaluated the uptake of ^{125}I IQ (1). High ^{125}I IQ uptake was observed in both CD133– and $CD133^+$ cells (63.6 ± 4.9% *versus* 43.5 ± 2.8%; n = 4/group). No explanation was given for the higher uptake in CD133– than in $CD133^+$ cells.

When compared with ^{18}F-FDG, the cell uptake of ^{125}I IQ was higher than that of ^{18}F-FDG in $CD133^+$ MG456 cells (1.3 ± 0.1%, 1.3 ± 0.1%, 1.7 ± 0.2%, and 1.8 ± 0.1% at 0.5, 1, 2, and 4 h, respectively for ^{18}F-FDG; $P < 0.001$ for all time points) (1). When assayed in phosphate-buffered saline to assess uptake in the absence of glucose in the media, ^{125}I IQ uptake was modestly reduced but remained significantly higher compared to ^{18}F-FDG (55.0 ± 2.5% *versus* 13.7 ± 6.2% at 4 h; $P < 0.001$). For all of these cell assays, cell viability remained >95% after the radiotracer uptake incubation period.

Animal Studies

Rodents

[PubMed]

Biodistribution studies were performed in C57/B6 mice (n = 5/time point) after tail vein injection of ^{125}I IQ (0.74 MBq (20 μCi)) (1). Mice were euthanized at 1, 4, and 24 h after administration, and uptake in organs was expressed as a percent of injected dose per gram (% ID/g). The biodistribution results showed that the primary route of ^{125}I IQ clearance was through urinary excretion. The initial uptake in the lungs, kidneys, adrenals, and liver cleared over the subsequent 24 h. The uptake in brain was initially low (0.2 ± 0.03% ID/g at 1 h; n = 5), and remained low (0.1 ± 0.01% ID/g at 24 h; n = 5).

The radiation exposure in humans for ^{123}I IQ and ^{131}I IQ was estimated on the basis of the tissue radioactivity from the biodistribution studies of ^{125}I IQ in mice (n = 5/time point) (1). The whole-body effective dose equivalent for ^{123}I IQ was estimated to be ~0.032 and ~0.039 mSv/MBq (0.11 and 0.14 rem/mCi) for males and females, respectively. For ^{131}I IQ, these values were 0.67 and 0.80 mSv/MBq (2.36 and 2.81 rem/mCi) for males and females, respectively.

Whole-body single-photon emission computed tomography (SPECT) was performed at 2–4 h after intravenous injection of ~1.85–3.7 MBq (~50–100 μCi) ^{123}I IQ into mice bearing MG456 brain tumors (1). None of the small intracranial tumors (n = 4) could be visualized with SPECT imaging. Autoradiography confirmed the presence of small tumors (~1 mm in shortest diameter), and gamma counting showed overall low uptake in the entire brain specimens (0.11 ± 0.01% ID/g; n = 4). All of the large intracranial tumors (n = 3) were visualized by imaging and detected with autoradiography and histology. For large tumors that could be well excised from adjacent brain, the ^{125}I IQ uptake was modest (2.3 ± 0.48% ID/g; n = 5) in a separate study (no details described).

Imaging in normal control mice (n = 4) confirmed low uptake in the brain, modest activity in the lungs and intestine, and high uptake in the genitourinary system. ^{123}I IQ uptake in normal brain tissue could not be visualized. Eyes (a known site of ALDH1 expression) were visualized on all ^{123}I IQ imaging studies, and this was confirmed in all subsequent mouse imaging studies with ^{125}I IQ and with gamma counting of the excised eyes (2.5 ± 0.21%; n = 3 mice).

In summary, Chin et al. observed high uptake of IQ in tumor cells with high ALDH1 activity *in vitro* and relatively low uptake in normal brains *in vivo* (1). However, the uptake in the brain tumors was also low, producing relatively low contrast on images. The investigators attributed the low contrast to several possible factors, including rapid renal excretion, relatively high uptake in soft tissues such as muscle, and suboptimal SPECT imaging parameters. Although the mechanism of cellular uptake for IQ is unknown, passive diffusion with lysosomal retention is considered to be the leading putative mechanism (1).

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.

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