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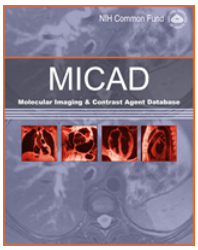

Ioxilan carbonate particles

IX-C particles

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Chemical name:	Ioxilan carbonate particles
Abbreviated name:	IX-C particles
Synonym:	Cyclic carbonate particles of ioxilan
Agent Category:	Compound
Target:	Reticuloendothelial system (RES) phagocytic cells
Target Category:	Phagocytosis
Method of detection:	Computed tomography (CT) and Planar X-ray
Source of signal:	Iodine (I)
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals

Background

[PubMed]

Ioxilan carbonate particles (IX-C particles) are X-ray contrast agent preparations developed for contrast enhancement of the liver in computed tomography (CT) imaging (1-3). Water-soluble, intravenous ioxilan injection is commercially available as an X-ray contrast agent for excretory urography and contrast enhanced computed tomographic (CECT) imaging of the head and body. However, IX-C as insoluble particles is not commercially available.

X-ray imaging (planar and tomographic) techniques depend on tissue density differences that provide the image contrast produced by X-ray attenuation between the area of interest and surrounding tissues (4). Contrast enhancement (opacification) with use of contrast agents increases the degree of contrast and improves the differentiation of pathologic processes from normal tissues. Because iodine, an element of high atomic density, causes high attenuation of X-rays within the diagnostic energy spectrum, water-soluble and reasonably safe iodinated contrast agents in intravenous injectable forms have been developed for clinical applications (5, 6).

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Water-soluble, intravenous X-ray contrast agents are generally organic iodine compounds that contain one or more tri-iodinated benzene rings. When injected intravenously, they are largely distributed in the extracellular fluid space and excreted unchanged by the kidneys. Contrast enhancement of a region of interest depends on the route of administration, delivery of the agent to the area by blood flow, and the final iodine concentration in the region (7, 8). There are two basic types of these compounds: ionic and nonionic agents (9).

Rapid i.v. injection of water-soluble X-ray contrast agents can be performed with dynamic computed tomography to improve the detectability of liver lesions (1-3). However, there are many limitations associated with this approach. Particulate contrast media have also been developed for selective opacification of the liver. This approach is based on the fact that particles are effectively taken up by the phagocytic cells (Kupffer cells) of the reticuloendothelial system (RES). Several particulate contrast agents have been developed. These particulate contrast agents can be classified into three groups: 1) emulsion of liposoluble oil; 2) encapsulation of water-soluble X-ray contrast agents in liposomes or polymeric microspheres; and 3) the lipophilic prodrugs derived from water-soluble contrast agents (1, 10). As a low-osmolar nonionic monomer, ioxilan was developed in an effort to increase the safety and tolerance of X-ray contrast agents (11, 12). The development of ioxilan was based on the belief that the introduction of a double methylene as a hydrophobic region and masking it with a hydrophilic hydroxyl group could lower the osmolality without adversely affecting the biological tolerance (13). Li et al. (1) prepared a biodegradable IX-C particle preparation based on the cyclic carbonate of ioxilan. IX-C particles serve as the prodrug of ioxilan that is targeted to the RES phagocytic cells. It is expected that IX-C particles are degraded inside the phagocytic cells to release the original nonionic, water-soluble ioxilan.

Synthesis

[PubMed]

Li et al. (1) prepared IX-C particles by a solvent extraction/evaporation method. IX-C was initially prepared by mixing carbonyldiimidazole with ioxilan in dimethyl sulfoxide (DMSO) over a period of 30 min (14). The mixture was then stirred at 70 °C overnight. A catalytic amount of sodium methoxide was added, and the reaction was terminated by diluting the DMSO with methylene chloride and washing with cold water. The yield of IX-C was 50%. IX-C obtained from this procedure was dissolved in methylene chloride and acetone (3:1 v/v). The IX-C solution was added to an aqueous solution of polyvinyl alcohol (PVA) and emulsified with a tissue homogenizer for 1 min. The mixture was then stirred at 400 rpm for 4 hrs. The resulting emulsion was centrifuged at 3,000 rpm, resuspended in distilled water, filtered by a 5-μm filter, and finally centrifuged again. This process was repeated three times to produce particles in the size between 0.36 to 5.54 μm (97%). For preparing particles with a narrower size distribution, the particles were separated further by density gradient centrifugation using colloidal suspension of silica (Percoll). These particles were suspended in a gradient system composed of pure water, 50% Percoll in water, and 100% Percoll. The suspension was centrifuged at 1,000 rpm for 10 min. The microparticles in the middle layer were in the size between 0.64 to 4.17 μm. These microparticles were washed three times in water by centrifugation (3,000 rpm for 10 min). When IX-C was dissolved in dimethylformamide and emulsified into an aqueous solution of PVA, IX-C nanoparticles in the size between 158 and 433 nm (97%) were formed. These particles were collected and washed with water by centrifugation at 10,000 rpm for 10 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Li et al. (1) used the scanning electron microscope and submicron particle analyzer to examine the IX-C microparticles. The microparticle preparation had an average diameter of 1-2 μm, and 95% are ranging between 0.6 and 2.0 μm. These particles were spherical with smooth surfaces, and the iodine content was 45%. In another similar study, Li et al. (3) reported that the IX-C nanoparticles had an average diameter of 290-300 nm

In a stability study of the IX-C microparticles (1), no immediate particle aggregation was observed when the microparticles were suspended in saline or in 0.1% Tween 80 solution. IX-C microparticles started to crumble and disintegrate after incubated in saline at 37 °C for 2 wks. The particles were also stable when first mixed with the slightly acidic rat or rabbit plasma at 37 °C. In 6 days, these particles were completely dissolved in plasma. The IX-C microparticles were completely dissolved in 0.1 N sodium hydroxide at 37 °C within 1 h. Using reverse-phase high performance liquid chromatography (HPLC) analysis and Fast Atom Bombardment Mass spectroscopy, it was shown that the degradation of IX-C particles yielded ioxilan and carbon dioxide.

Animal Studies

Rodents

[PubMed]

Acute toxicity studies of IX-C microparticles were tested in mice, and the median lethal dose was 3.1 g/kg (1.4 g I/kg) body weight for male and 2.6 g (1.2 g I/kg) for female (1). In a kidney toxicity study in rats, both IX-C microparticles and nanoparticles (100 mg/kg i.v.) caused significant increases in blood urea nitrogen (BUN) and creatinine levels in one day after injection (2). These increases induced by IX-C nanoparticles were higher than those by microparticles. In rats injected with IX-C nanoparticles, histologic and microscopic studies of the kidneys revealed proximal tubule damages.

Li et al. (3) studied the biodistribution of IX-C microparticles and nanoparticles (50 mg I/kg) in rats. The tissue samples were analyzed by the inductively coupled plasma-mass spectrometry for iodine concentrations and HPLC for ioxilan concentrations. For IX-C nanoparticles, there was a substantial retention in the blood and liver after 5 min. The blood concentration was higher. Iodine levels in the live rand spleen remained unchanged for the next six h. There was a gradual decline in the liver concentration to about 10% of the injected dose at 24 h. There was also a decrease of iodine in the blood and a corresponding increase of iodine in the kidney. The iodine concentration the kidney increased to a peak at two h after administration. The kidney concentration decreased to a negligible level at 24 h. The blood kinetics of IX-C microparticles was similar to that of nanoparticles. Microparticles had a significantly lower liver concentration than that of nanoparticles, but the spleen concentration was significantly higher. The kidney uptake of IX-C or its degradation product of the nanoparticles was more than six times than that of the microparticles.

Other Non-Primate Mammals

[PubMed]

Li et al. (1) conducted CT imaging studies of IX-C microparticles in normal and VX2 liver tumor bearing rabbits. After i.v. doses of 100, 200, and 270 mg I/kg, the maximum liver attenuation enhancements (ΔHU) at 30 min after injection were 23, 38, and 110, respectively. At 200 mg I/kg, the ΔHU for the spleen was 245 immediately after injection. In the VX2 liver tumor rabbits, the tumors without contrast were barely detectable in all animals. After injection of 200 mg I/kg IX-C microparticles, the tumors were clearly visible for up to two h. There was an increase in the attenuation difference of 35 HU between the liver and the tumor.

In a kidney toxicity study, Li et al. (2) reported that the BUN and creatinine levels did not change significantly from levels before i.v. injection of 200 mg I/kg IX-C microparticles. No significantly lesions on the kidneys were observed.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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