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Technical note

Drug metabolism: Comparison of biodistribution profile of holmium in three different compositions in healthy Wistar rats

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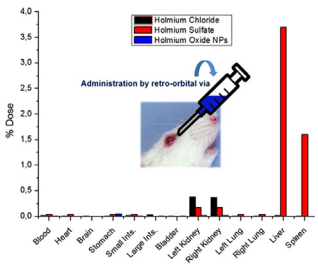
HIGHLIGHTS

- This article brings the biodistribution of holmium in 3 different compositions.
- The results, as a technical note may help other researchers around the world to elucidate the mechanism (biological behavior) and the best strategy to use holmium as radiopharmaceutical.

GRAPHICAL ABSTRACT



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ABSTRACT

Radioisotope holmium is a candidate to be used in cancer treatment and diagnosis. There are different holmium salts and they present distinct solubility and consequently different biodistribution profiles. In this work, we aimed to evaluate the biodistribution profiles of two holmium salts (chloride and sulfate) and holmium nanoparticles (oxide) through an *in vivo* biodistribution assay using animal model. Samples were labeled with technetium-99m and administered in Wistar rats by retro-orbital route. Holmium chloride is highly soluble in water and it was quickly filtered by the kidneys while holmium sulfate that presents lower solubility in water was mainly found in the liver and the spleen. However, both the salts showed a similar biodistribution profile. On the other hand, holmium oxide showed a very different biodistribution profile since it seemed to interact with all organs. Due to its particle size range (approximately 100 nm) it was not intensively filtered by the kidneys being found in high quantities in many organs, for this reason its use as a nanoradiopharmaceutical could be promising in the oncology field.

1. Introduction

Physical characteristics of the radionuclides such as the type of radioactive emission and half-life should determine their use in nuclear medicine (diagnosis, therapeutics and theranostics) (Albernaz Mde et al., 2014; Carvalho Patricio et al., 2013). Radionuclides could be administered to patients in their free form or encapsulated in a nanostructure, e.g., polymeric nanoparticles, liposomes and dendrimers, to improve solubility and bioavailability of the drug. In addition, radionuclides could label drugs or nanostructures containing the drug which make radiolabeling a widely used technique to understand the pharmacokinetics and

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pharmacodynamics of drugs administered by several routes (Cerqueira-Coutinho et al., 2015).

There are many challenges related to the use of radiopharmaceuticals in cancer therapy, one that could be easily addressed is the limited entrance of the drug in the abnormal tissue or organ. Thus, a strategy that could improve drug targeting and tissue retention with low toxicity would optimize cancerdiagnosis and treatment (Di Pasqua et al., 2013, 2012).

Drugs with different solubility would present different bioavailability since this last one is related with the transit of the drugs through tissues, crossing membranes to reach bloodstream (Hamoudeh et al., 2008). For this reason, many factors have to be considered when administering drugs to the patient: solubility, molecule size and charges, interaction with plasmatic proteins, stability and biodistribution (Leite Diniz et al., 2010).

The therapeutic radionuclide holmium is an available candidate to be used against many types of cancer and it is also an effective choice for treating ovarian cancer metastases (Munaweera et al., 2014; Omar et al., 2015).

Holmium salts present different solubility and for this reason different biodistribution.

In this context, the main objective of this study was to evaluate the biodistribution profile of two holmium salts(chloride and sulfate) and compare it with holmium nanoparticles (oxide)(all labeled with technetium-99m), which were administered to Wistar rats by retro-orbital route.

2. Materials and methods

2.1. Materials

Holmium chloride, holmium sulfate (both are salts) and holmium oxide (insoluble nanoparticle) were purchased from Sigma-Aldrich.

2.2. Labeling of holmium salts and nanoparticles with Technetium-99m

Samples were prepared by adding each salt (holmium chloride and sulfate) and the nanoparticles (holmium oxide) to NaCl 0.9 wt% aqueous solution by vigorous stirring, reaching a final concentration of 30 μg/mL (Table 1a and b). The salts were soluble in the NaCl solution while holmium nanoparticles, insoluble due to its oxide nature, were dispersed and the sample was slightly cloudy. According to the supplier, holmium nanoparticles present less than 100 nm of diameter, which enables to form a homogeneous dispersion when stirred. Then 150 μL of each solution and the dispersion were labeled with Technetium-99m by direct labeling process (Patricio et al., 2015; Pinto et al., 2014). The samples

Table 1
a) and b) Preparation of samples and labeling process with Technetium-99m.

a)

Salt/NPs	Final concentrations of the salts after the addition of NaCl 0.9 wt%
Holmium chloride	30 μg/mL
Holmium sulphate	30 μg/mL
Holmium oxide NPs	It was insoluble, thus forming a slightly cloudy dispersion of 30 μg/mL

b)

Salt solutions and NPs dispersion	1st Step	2nd Step
150 μL of each solution and the dispersion were direct labeled with $Na^{99m}TcO_4^-$	80 μg/mL solution of stannous chloride for 20 min at room temperature.	Then this mixture was incubated with a solution of 3.7 MBq (0.3 mL Technetium-99m in NaCl 0.9% aqueous solution) for 10 min at room temperature.