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Short communication

Preparation of ^{188}Re-HEDP as a bone tumor radionuclide therapeutic

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Introduction

^{188}Re-HEDP (hydroxyethylidenediphosphonate) is an osteotropic radiopharmaceutical used in palliative treatment of primary and metastatic bone tumors, in addition to external beam therapy (Liepe, 2018). According to its chemical structure, it is a complex compound composed of a bisphosphonate ligand molecule that incorporates an atom of the radioactive ^{188}Re, which is a beta-emitting radionuclide whose physical characteristics are suitable for its therapeutic use. The energy of its gamma radiation is very similar to the gamma radiation of technetium-99m, which allows monitoring its biodistribution with conventional gamma cameras. Another important feature of ^{188}Re is that it is a generator product obtained from ^{188}W/^{188}Re generator without the presence of a "carrier" which facilitates its widespread use (Lee et al., 2009). The main aim was to present the preparation and quality control of ^{188}Re-HEDP for clinical application in therapeutic nuclear medicine.

Materials and methods

Obtaining ^{188}Re

Rhenium [^{188}Re] was obtained from an alumina-based ^{188}W/^{188}Re generator (Oak Ridge National Laboratories, USA and MAP Medical, Finland) by elution with 0.9% NaCl solution. The principle by which the generator operates is similar to a ^{99}Mo/^{99m}Tc generator (Vucina 2002). The parent isotope (^{188}W) is chemically adsorbed on the chromatographic carrier-Al_2O_3 and the offspring isotope (^{188}Re) is separated by elution with saline (0.9% NaCl).

The radiopharmaceutical ^{188}Re-HEDP was prepared by in-house developed HEDP solution.

Preparation of HEDP kit

The HEDP kit contains: Na_2HEDP, gentisic acid and $SnCl_2$, dissolved in 0.9% NaCl. The compounding is performed aseptically in a LAF cabinet. Firstly, Na_2HDP (166 mg) and gentisic acid (60 mg) are dissolved in 10 mL of nitrogenous 0.9% NaCl. During constant stirring of the previous solution, $SnCl_2$ (77 mg) was added. This solution, with a pH of approximately 1, is sterilized through a 0.22 μm Millipore filter. The solution is dispensed into multidose sterile vials, 1 mL in each. The vials are stored frozen between -20 ºC and -70 ºC (Lin et al., 1999).

Radioactive labeling of HEDP with ^{188}Re

^{188}Re-HEDP is prepared by adding 1-3 mL of $^{188}ReO_4$- to the vial containing 1 mL HEDP cold kit with an activity of 1-4 GBq, and 20 mL of "carrier"[1] (Lepareur et al., 2019), which is a solution of stable Re in the form of NH_4ReO_4. After mixing intensively for 1-5 minutes, the mixture is placed in a 100 ºC water bath for 30 minutes. The solution is then cooled at room temperature under running cold water, and 2 mL of Na-acetate buffer is added, adjusting the pH to 5-6 (Lin et al., 1999).

Preparation of the "carrier" solution: 20g NH_4ReO_4 (Aldrich Chemical Co.) are dissolved in 2 mL of previously nitrogenated 0.9% NaCl. This solution is stored at + 4 ºC.

Determination of radiochemical purity of ^{188} Re-HEDP

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The radiochemical purity of ^{188}Re-HEDP was performed by instant thin layer chromatography (ITLC), using ITLC-Silicagel strips developed in 95% acetone (Lin et al., 1999). In this chromatographic system, the ^{188}Re - HEDP complex remains at the application site (Rf ≈0.0-0.1), while the free perrenate migrates with the solvent (Rf ≈0.9-1.0).

Results and discussion

In our study we evaluated the bone-targeted radiopharmaceutical for therapeutic use - ^{188}Re-HEDP, which has been proposed as an alternative to ^{186}Re-HEDP (Liepe, 2018). The physical properties, the compounding method and the lower cost make ^{188}Re suitable for use in nuclear medical centers of different types.

Following the prescribed protocol, we labeled the HEDP kit with ^{188}Re, and performed the quality control. First, by visual inspection, it was concluded that the preparation was clear, without turbidity and visible particles, while the pH was approximately 6.5. In terms of radiochemical purity, the percentage of ^{188}Re HEDP complex was 98.87% (SD = 0.21), obtained by ITLC.

As the chemical properties of ^{188}Re (VII) perrenate and ^{99m}Tc(VII) pertechnetate are very similar, the choice of therapeutic ^{188}Re labeling ligands is based on the experience gained from ^{99m}Tc-labeled diagnostic radiopharmaceuticals (Deutsch et al., 1986).

However, certain differences in the chemical properties of technetium and rhenium complexes affect their biological behavior, which imposes the need for a different approach to their preparation. Due to the fact that rhenium is chemically much more stable in higher valence states, it is more difficult to reduce than technetium. Additionally, rhenium radiopharmaceuticals have a greater tendency to reoxidize in perrenate than technetium radiopharmaceutical analogues in pertechnetate, which affects the biodistribution of the radiopharmaceutical (Vucina, 2002).

During the initial preparation of ^{188}Re-HEDP, a larger excess of tin ions is used for the reduction reaction to be more complete and faster. Due to the large amount of tin ions, a proportionally larger amount of HEDP ligand is needed, because otherwise there would be precipitation of tin salts in a neutral environment. Therefore, the Sn-HEDP kit for the preparation of ^{188}Re(Sn)HEDP contains about ten times more Sn(II)HEDP in comparison to technetium labeling HEDP kit (Lin et al., 1999).

Another feature in the preparation of ^{188}Re-HEDP is the incubation in a boiling water bath for about 30 minutes. This procedure is based on previous studies performed in order to determine the conditions for preparation of ^{186}Re-HEDP. The study of Kothari et al. (Kothari et al., 1999) showed that the ^{186}Re-HEDP complex is initially formed in a high percentage (>98%), regardless of whether the incubation takes place at room temperature or in a boiling water bath (about 100 °C). However, the stability study showed that the formed complex is stable only if the incubation takes place in a boiling water bath for 30 minutes. It is assumed that in this way conditions are created for decomposition of the metastable ^{188}Re-HEDP complexes, but also of the other formed complexes of the previously reduced rhenium complex (Lin et al., 1999).

Conclusion

Based on the results obtained from our study, it can be concluded that the prescribed compounding conditions (composition and concentration of chemical components, temperature and incubation time) are optimal for the initial formation of the chelating complex ^{188}Re-HEDP in a high percentage (> 98%).

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