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*Short communication*

# Stability study of $^{188}$Re-HEDP as a radionuclide therapeutical for bone pain palliation

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## Introduction

Bisphosphonates are ligands containing the chemical P-C-P bond, which make these molecules resistant to the hydrolytic action of polyphosphatases and hence express high in vivo stability (Body, 2003). Our stability study was performed in order to determine the optimal storage conditions of a single dose radiopharmaceutical, when not applied to a patient immediately after the preparation. Given that the radiopharmaceutical is intended for palliative treatment of patients with malignant diseases, whose condition often does not allow transport to nuclear medicine centers, there is a need for the therapeutic dose to be transported to the institution where the patient is hospitalized (Lepareur et al., 2019). With this study we wanted to examine the conditions in which the transported radiopharmaceutical would remain stable for the longest time, after its separation in syringe as individual patient dose. It is known from the literature that the environmental factors which affect the stability of the rhenium-diphosphonate complexes are temperature and light (Lin et al., 1999).

## Materials and methods

Radioactive labeling of HEDP with $^{188}$Re was performed by the protocol described elsewhere (Lin et al., 1999). The product was exposed to different environmental conditions, namely: at temperature of 20-25$^{o}$C and 4$^{o}$C in the dark, as well as at 20-25$^{o}$C in the light. Because saline is used for diluting radiopharmaceuticals in single doses, the stability in 0.9% NaCl was investigated as well. In order to assess the stability of $^{188}$Re-HEDP complex in the bloodstream after its intravenous administration, the stability of the radiopharmaceutical mixed with serum at 37$^{o}$C was examined.

Assessments of the radiochemical impurity were performed at 1 hour, 3, 6, 24, 48 and 72 hours after preparation of the radionuclide therapeutical by standard procedure (Kothari et al., 1999).

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

The radiochemical purity of $^{188}$Re-HEDP was performed by instant thin layer chromatography (ITLC), using ITLC-Silicagel strips developed in 95% acetone. 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). ITLC analyzes were performed in triplicates and their mean value was calculated.

## Results and discussion

The radiopharmaceutical stability study gave the most optimal conditions in which the $^{188}$Re-HEDP complex remains stable for the longest time. The results showed that the complex is most stable in the first 3 hours after preparation, if stored at +4$^{o}$C in dark. Chromatographic analyzes performed 24 hours after preparation showed that the percentage of the complex dropped below 60%, with the exception of the 0.9% NaCl sample stored at + 4$^{o}$C in dark, where values of 71.89% were obtained (SD = 4.9).

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After 48 hours, the highest decomposition of the complex was observed in the samples stored at + 20°C in 0.9% NaCl in light - 37.65% (SD = 0.07) and 31.22% in dark (SD = 2.03), while the highest percentage of radioactive complex was obtained in the preparation stored at +4°C in 0.9% NaCl in the dark (65.26%, SD = 0.71). The highest stability of the complex after 72 hours of preparation showed the preparation stored at +4°C in 0.9% NaCl in dark (58.14%, SD =1.28).

The results of our stability study showed that $^{188}$Re-HEDP prepared according the standard prescription, has less stability when dissolved with saline after preparation at 25°C. According to other similar studies (Lin WY. et al., 1999), in radiopharmaceutical not dissolved in saline and stored at 25°C, the percentage of $^{188}$Re-HEDP complex is 92.3% after 24 hours. After 72 hours the percentage of $^{188}$Re-HEDP complex dropped to 89.6% (Lin et al., 1999).

In our study, the mean value of the initial percentage of the complex was 98.87%, which is a higher value than the initial percentage of the complex obtained in the cited study (> 95%). After 24 hours from the preparation of the preparation, the percentage of complex has dropped below 60% with the exception of the sample stored at + 4°C in 0.9% NaCl in dark, where an average value of 71.89% was obtained. After 72 hours of preparation, the greatest stability of the complex was shown by the preparation stored at +4°C in 0.9% NaCl in e dark. In that sample, an average value of 58.14% was obtained, which is a significantly lower percentage compared to the values from the previously cited study (89.6%).

The results from our stability study indicate that the volume reconstitution of $^{188}$Re-HEDP with saline makes the formed complex unstable. The reason for destabilization of the $^{188}$Re-HEDP complex is the reoxidation of $^{188}$Re-HEDP to $^{188}ReO_4^-$ under the action of oxygen which is introduced into the radiopharmaceutical. In general, the largest amount of oxygen is introduced when the contents of the radiopharmaceutical are drawn into a syringe, but also a significant part is the oxygen dissolved in the saline used for volume reconstitution.

The fact that the formed complex remains stable for the longest time if the product is stored at low temperature (+4°C), is explained by the fact that the chemical reactivity between oxygen and the rhenium complex is slowed down when the temperature of the reaction medium is low.

Our stability study showed that light had no effect on the stability of the $^{188}$Re-HEDP complex.

The results for the stability of the complex in serum showed that in the first 6 hours the radiopharmaceutical mixed with serum has greater stability compared to the radiopharmaceutical stored in other conditions. However, after 24 hours, the percentage of the complex is lower compared to that part which is stored at + 4°C in 0.9% NaCl in dark, but still higher than the preparation stored at +20°C in 0.9% NaCl in dark and light. These results can be explained by the presence of biological antioxidants in the serum that reduce the reoxidation of the $^{188}$Re-HEDP complex. Because their amount in the serum is limited, after 24 hours their concentration decreases, which reduces their protective effect.

## Conclusion

The initially formed complex of $^{188}$Re-HEDP loses the radiochemical stability with dispensing of individual doses and volume adjustment with saline. The $^{188}$Re-HEDP complex in a single dose is most stable for 1-3 hours (≈ 95%), if the preparation is stored at + 4°C. The light has no effect on the stability of the initially formed $^{188}$Re-HEDP complex. Single patient doses of this product for the radionuclide treatment of bone metastases should be transported refrigerated within 3 hours of preparation.

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