Preparation and biological evaluation of $^{186/188}$Re-HEDP as a new cocktail radiopharmaceutical for palliative treatment of osseous metastases in wild type rat

Original Article

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ABSTRACT

Introduction: The palliative care in patients with bone metastasis includes variety of techniques such as conventional analgesics, surgery, external beam radiotherapy, hormone therapy, chemotherapy and using bone-seeking radiopharmaceuticals. Even some of the recent works used combined methods like chemotherapy and radionuclide therapy or using radionuclide therapy as adjuvant to external beam therapy or even using tandem 2 separate radiopharmaceuticals. In line with combined methods, due to the improved efficacy of two radioisotopes with complementary properties in treatment, in this study we proposed using compositional radiopharmaceuticals as a new idea. In this study as a new idea the combined radionuclide therapy have been investigated with utilizing ^{188}Re and ^{186}Re complementary features in the $^{188/186}$Re-HEDP cocktail to achieve the maximum efficacy.

Methods: ^{186}Re and ^{188}Re have been produced simultaneously with identical activities by natural rhenium irradiation. Produced $^{188/186}$Re-HEDP with high radiochemical purity was administered intravenously to rats. Biodistribution data were collected at 2, 4, 24, 48 and 72 hours post injection and scintigraphic images were taken at 24 hours after administration of radiopharmaceutical.

Results: $^{188/186}$Re-HEDP was prepared with radiochemical purity of nearly 99%. Its biodistribution data showed high uptake and durability in the skeletal tissues without significant uptake in other major organs.

Conclusion: The study results demonstrate that the combination of ^{186}Re and ^{188}Re in cocktail radiopharmaceutical form is achievable and safe. The complementary features of ^{188}Re and ^{186}Re, due to their different energies, half-lives and penetration ranges can lead to more efficacy in bone metastases treatment.

Key words: $^{188/186}$Re–HEDP; Cocktail radiopharmaceutical; Radionuclide therapy; Pain palliation; Bone metastasis

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INTRODUCTION

Metastasis or spread of cancer cells from primary site to different organs including bone is the main cause of mortality in different malignancies. These cells move through the lymph system or the bloodstream and bony structures are the main site of metastatic involvement.

The relative occurrence of bone metastasis in patients with advanced metastatic stages in different types of tumor is: 65-75% in breast; 65-75% in prostate; 60% in thyroid; 30-40% in lung; 40% in bladder; 20-25% in renal cell carcinoma and 14-45% in melanoma [1].

The most frequently problems, which patients face, are intolerable pain, bone fractures, nerve compression, hypercalcemia, spinal cord injury, bone marrow aplasia and most importantly, reduced quality of life [2-4].

Some therapies, such as chemotherapy, external beam radiotherapy, hormonal therapy, painkillers, bisphosphonates and bone-seeking radiopharmaceuticals are used to help to relief pain and improve quality life in patients with bone metastases [5-7].

Considerable preferences of bone radionuclide therapy is its ability to effect on multiple sites of the disease applying the therapeutic effect in earlier phases of metastatic disease, preferably associated with simplicity of administration, the combination with the other treatments and its repeatability [8].

Numerous beta emitter radioisotopes like ^{177}Lu, ^{153}Sm, ^{186}Re, ^{188}Re have been utilized for this treatment procedure. Among these beta-emitting radioisotopes, there are two radioisotopes of ^{186}Re and ^{188}Re with different properties, which have been examined to achieve better treatment results.

Delivering high doses to tumors with lower unwanted radiation to other organs and a faster clearance rate is the ultimate goal in treating bone metastases. One of the ligands to produce bone-seeking radiopharmaceuticals is 1-hydroxyethylidene-1,1-diphosphonic acid (HEDP) (Figure 1).

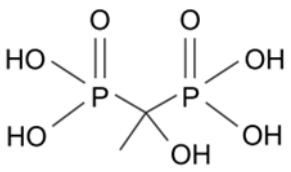

Fig 1. Chemical structure of HEDP.

The initial report of the possible use of ^{186}Re-HEDP in the treatment of bone metastases was in 1979 [9] and the first clinical experiment was done in 1990 [10]. From that time many works have been done in different evaluation steps of including efforts in producing ^{186}Re-HEDP kit to reach higher quality with different experiments like changing its constituent components [11, 12] and different radiochemical tests [13, 14] to achieve newer clinical evaluations and more recent analytical assessments [15-18].

In 1998, Maxon et al. demonstrate safe and efficient use of ^{188}Re-HEDP in patients with osseous metastases [19]. Subsequently, therapeutic efficiency of this agent with improved quality of life was demonstrated [20-27].

Ranjbar et al. prepared ^{153}Sm/^{177}Lu-EDTMP mixture as a cocktail radiopharmaceutical and evaluated its usefulness in wild-type rats in detail [28]. ^{153}Sm emits beta particles with higher energies and longer range in tissues, which may be preferable for larger tumors, while ^{177}Lu with shorter beta particle range and longer half-life may be preferable for smaller tumors. Because ^{177}Lu has a longer half-life, it will take longer to deliver the same doses as ^{153}Sm. Therefore, in patients with tumors of various sizes, a cocktail might be ideal as a combination of radionuclides, accordingly, the mixture of ^{177}Lu and ^{153}Sm as ^{153}Sm/^{177}Lu-EDTMP cocktail was proposed as a potentially efficient and safe approach [28].

Furthermore, Alavi et al. administered ^{153}Sm/^{177}Lu-EDTMP to human patients and reported satisfactory results [29]. They also did not report any early hematological toxicity, bone marrow suppression or other adverse effects when using cocktail radiopharmaceutical in compare of standalone application of ^{153}Sm-EDTMP or ^{177}Lu-EDTMP and finally they concluded that ^{153}Sm/^{177}Lu-EDTMP cocktail is a safe and effective option in patients with skeletal metastases for bone pain palliation and improvement of their quality of life [29]. Clinically, by agent such as ^{153}Sm with shorter half-life, pain relief begins earlier compared with radiopharmaceuticals with longer half-life like ^{177}Lu while the duration of pain reduction seems to be shorter. Currently, ^{177}Lu with its longer half-life is considered a more durable agent to achieve pain reduction and even therapeutic effect.

^{186}Re ($t_{1/2}$ = 3.8 d, $E_{\beta max}$ = 1.07 MeV, E_{γ} = 137 keV [9% abundance]) with longer half-life and lower beta energy is appropriate to irradiate smaller targets, over a longer period. On the other hand ^{188}Re ($t_{1/2}$ = 0.7 d, $E_{\beta max}$ = 2.12 MeV, E_{γ} = 155 keV [15% abundance]) with higher energy β- particles and lower half-life transmits its energy to the tumor at once and these features make it a good agent to irradiate large tumors. With regard to these complementary features of ^{188}Re and ^{186}Re, it is expected that with concomitant use, the synergistic therapeutic effects will be possibly achievable and the resultant complex might be known as a cocktail radiopharmaceutical with more advantages to treat and eradicate tumors.

The effectiveness of ^{188}Re and ^{186}Re in treatment of osseous metastatic disease and their potential for

increased efficiency when use in combination as cocktail radiopharmaceuticals, was the idea behind this work for production of rhenium compositional radiopharmaceutical. To achieve this goal, ^{188}Re and ^{186}Re have been produced simultaneously. Radiolabeling, quality control and biodistribution studies of $^{188/186}$Re-HEDP in rats are investigated. In order to make the comparison of each ^{188}Re and ^{186}Re radionuclides behavior simultaneously, the time/activity diagrams for the labeled compound in different organs are plotted and the results are discussed.

METHODS

The metallic natural rhenium powder (with purity 99.99%) target was provided from Merck company. Rhenium medical radionuclides production were performed at the Tehran Research Reactor (TRR) using ^{185}Re(n,γ)^{186}Re and ^{187}Re(n,γ)^{188}Re. Freeze dried HEDP kit (composition: $SnCl_2$: 6mg, Ascorbic acid: 3 mg, HEDP: 40mg dissolved in 1 cc normal saline and lyophilized) was obtained from Pars Isotope Company, Iran. All other chemicals were purchased from Merck Company. A high purity germanium (HPGe) detector manufactured by ORTEC Company, with 40 % relative efficiency coupled to 8 K MCA system. Radio-chromatography was performed by counting Whatman papers using a thin layer chromatography scanner, Bioscan AR2000, Paris, France. Scintigraphic images were recorded using a dual-head digital SPECT gamma camera (GE Wipro, USA) with a low energy-high-resolution (LEHR) collimator.

Rhenium radioisotopes production

One mg of natural rhenium powder was weighted and sealed in quartz vial. The sample was irradiated for 4 days in neutron flux 3-4×10^{13} n/(cm^2s) and was cooled for 18 hours. These times are optimal times that have been calculated to achieve equal activities of ^{186}Re and ^{188}Re in our previous works [30, 31]. At the end of irradiating process ^{186}Re and ^{188}Re were produced with appropriate activities.

$HReO_4$ production

Following the production of rhenium radionuclides in the previous section, the sample was removed from the reactor and cooled for 18 hours. Then, the aluminum can and quartz capsule were unsealed.

After producing rhenium radioisotopes, first, the activated rhenium metal powder was dissolved completely in hydrogen peroxide by heating to produce perrhenic acid solution (0.1 cc of Hydrogen peroxide 30%, 40 °C, about 20 minutes). Next, quartz contents were poured into a vacuum vial and quartz was washed with 0.1cc of Hydrogen peroxide solution more and added to the vial. Then, the excess hydrogen peroxide is removed by heating, resulting in a yellow-colored, dry residue (vacuum evaporated by peristaltic pump, 90 °C for about 70 min). Finally, the residue dissolved in saline (0.9%) to produce the desired radioactivity concentration of [$^{188/186}$Re]$NaReO_4$.

Quality control

The analysis of gamma-ray emitting radionuclides to evaluate the main radionuclides and the presence of potential impurities were carried out using γ-ray spectroscopy with a high-purity germanium (HPGe) detector.

Radiolabeling process

HEDP kit was obtained from Pars Isotope Company. The kit was dissolved in the 0.5 cc saline completely. The mixture of [$^{188/186}$Re]$NaReO_4$ which its production procedure mentioned above, was added to the solution of HEDP in saline vial and was placed in boiling water for about half an hour until it got yellow dark. In order to reach the pH = 6, 3 cc sodium acetate buffer was added to the composition with different amounts over several steps.

Thin layer chromatography

In this research, to calculate the radiochemical purity and determine free perrhenate (ReO_4^-) and reduced rhenium (ReO_2) and $^{188/186}$Re-HEDP, two separate solutions of saline and acetone were used as mobile phases and Whatman paper No. 1, as a stationary phase.

Samples were spotted on Whatman paper No. 1 chromatography paper (12 cm long). The strips were placed in acetone and saline until the solvents reached to the top of the strips. The ITLC analysis was done using the chromatography system, which has been mentioned above.

Biodistribution studies

Male wistar rats with weights 210–330.4 g were used to evaluate of the $^{188/186}$Re-HEDP complex biodistribution after radiolabeling. Each rat received 200 µl of the complex with 444.4 µCi activities of ^{188}Re and ^{186}Re via the tail vein. The rats were killed at the end of 2, 4, 24, 48 and 72 hours post injection. Three rats were used for each time point. The organs were removed and weighted. The high-purity germanium detector (HPGe) was used to measure the accumulated activities in organs. Distribution of the activity in different organs was calculated as the percentage of injected activity per g of organ (% ID/g). Animal experiments were performed in accordance to the ethical principles and the national norms and

standards for conducting medical research in Iran (Approval ID: IR.PNU.REC.1398.050).

Imaging studies of $^{188/186}$Re-HEDP in rats

Scintigraphic imaging studies also have been done to investigate biodistribution behavior of $^{188/186}$Re-HEDP. Images were taken before sacrificing the rats at 24 h after injection of the radiopharmaceutical by a dual-head SPECT system. The gamma camera was previously calibrated for 137 and 155 keV gamma photons of ^{186}Re and ^{188}Re respectively. The mouse-to-high energy septa distance was 12 cm. The useful field of view (UFOV) was 540 × 400 mm^2 and the spatial resolution was 10 mm FWHM at the CFOV.

RESULTS AND DISCUSSION

Production and quality control of radioisotopes

^{186}Re and ^{188}Re were produced by natural rhenium powder irradiation in Tehran Research Reactor. The activated product was dissolved in hydrogen peroxide. After evaporating the sample, the dry product was dissolved in saline.

The precise activity determination of each radionuclide was done and the measured activity for each of the rhenium-186 and rhenium-188 radinuclides was equal to 10 mCi/cc. Radionuclide purity was investigated for the presence or absence of other probable radionuclides. Sample gamma spectrometry was performed using a coupled HPGe detector with a multichannel analyzer.

As shown in Figure 2, the energy peaks of 137 keV and 155 keV are related to rhenium-186 and rhenium-188, respectively. There are some other peaks like 478 keV and 633 keV, which are related to rhenium-188 with smaller intensities. In addition, the peaks with lower energies like 61 and 63 keV (related to both rhenium-186 and 188) and 59 keV (related to rhenium-186) can be seen and impurities are not observed.

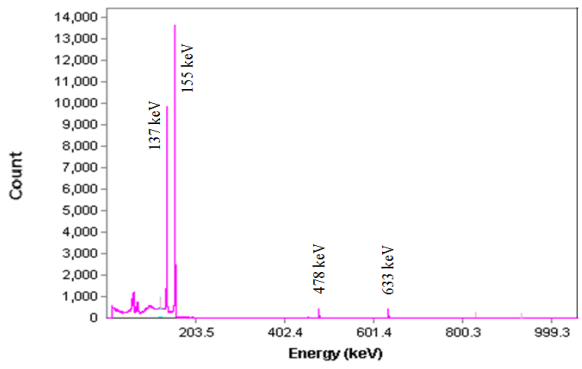

Fig 2. Gamma spectrum for [$^{188/186}$Re]$NaReO_4$ solution.

Preparation and quality control of $^{188/186}$Re-HEDP

The lypophilized HEDP kit was dissolved in saline to make mixing easier. The dissolved kit was added to [$^{188/186}$Re]$NaReO_4$ vial. With heating mixtures in boiling water for 30 min, it was seen that the content of vial gets yellow dark, which it indicates complementary procedure must be done successfully.

To evaluate free perrhenate (ReO_4^-), acetone was used as the mobile phase. In this system free perrhenate (ReO_4^-) moves with the mobile phase and in spotting point we have the $^{188/186}$Re-HEDP complex and reduced rhenium (ReO_2).

To determinate the amount of free ReO_2, sodium chloride 0.9% was used. In this system, the components, which move with mobile phase, are $^{188/186}$Re-HEDP and free ReO_4^- and ReO_2 remains at the application spot. Then the radiochemical purity was calculated. In this study, the radiochemical purity nearly 99% was achieved (Figure 3).

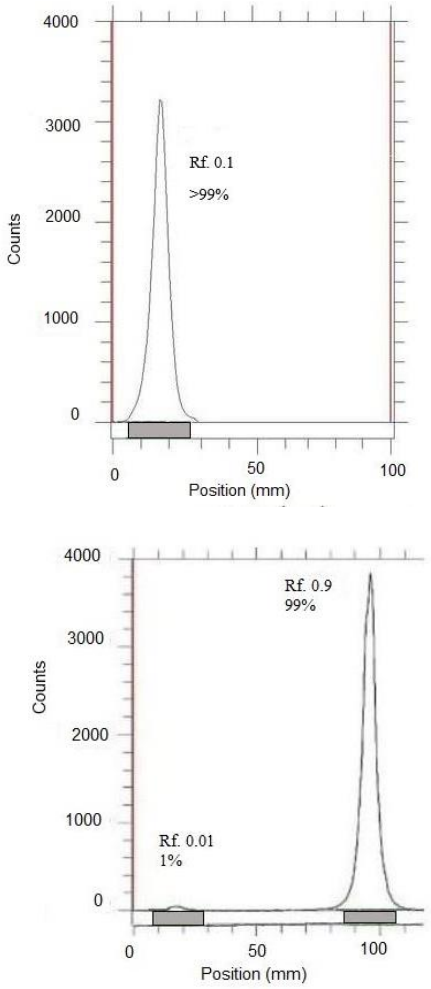

Fig 3. ITLC chromatograms of $^{188/186}$Re-HEDP in acetone (above) and in saline (below) with Whatman No. 1 paper.

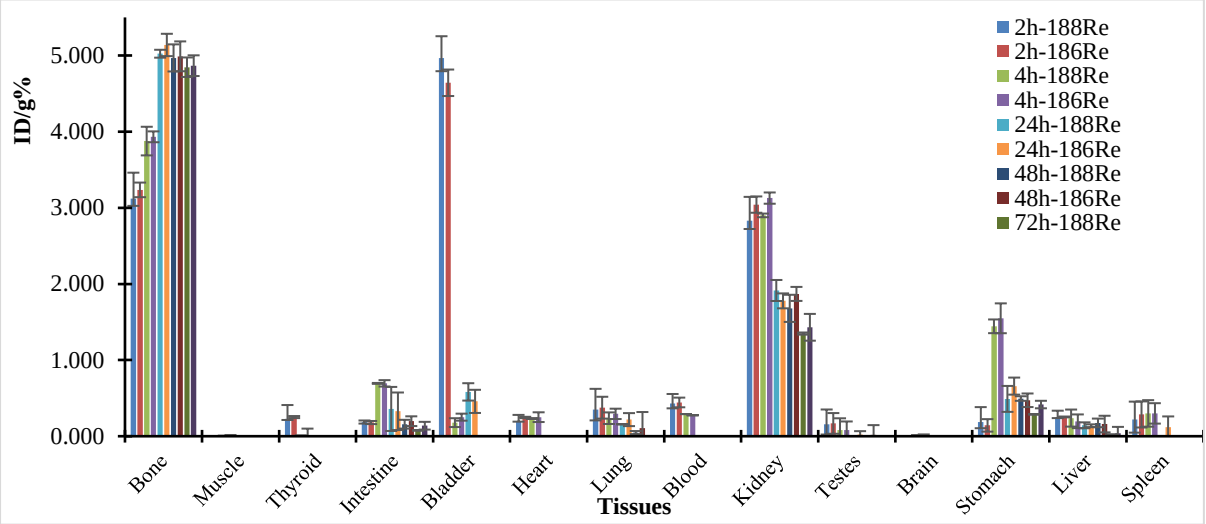

Fig 4. Biodistribution study of $^{188/186}$Re-HEDP in wild type rats.

Biodistribution studies

Concerning half-lives, the biodistribution evaluation of $^{188/186}$Re-HEDP up to 72 hours after injection was considered. The animals were sacrificed by CO_2 asphyxiation at 2, 4, 24, 48, 72 h after injection. Blood was drawn from the aorta then bone, liver, kidneys, stomach, lungs and other needed organs were carefully removed and weighted. The accumulated activities in organs were counted by HPGe to determine the percentage of injected dose per gram. These measurements were acquired from the area under the curve of 137 and 155 keV gamma photons of ^{186}Re and ^{188}Re respectively to calculate %ID per gram. The uptake of the $^{188/186}$Re-HEDP complex in the different organs of wistar rats, expressed as %ID per gram at different post injection times, is shown in Figure 4. The figure points out the following important results:

- As expected, $^{188/186}$Re-HEDP showed the highest uptake in the bone. In 2 hours after injection, the mixture showed appropriate uptake in the bone (femur). This increasing trend continued, until 24 hours when femur uptake reached to 5.023% and 5.138% ID/g for ^{188}Re and ^{186}Re, respectively.

- Bone uptake of $^{188/186}$Re-HEDP stayed almost unchanged during the study time. The reason for this is that the radiopharmaceutical was not cleared from the bone or re-accumulated in other organs.

- The kidneys were the second organ with highest tracer uptake.

- Liver as an important organ showed low %ID/g.

- Generally, the bladder uptake was low but in the first 2 hours, its %ID/g value was high which is because of the initial urinary excretion.

The rhenium accumulation in the stomach in research period is at acceptable level, decreasing with early approach to zero, however, nearly at the beginning of the study (4h) the %ID/g in this organ increases, which probably is due to the presence of the $^{188/186}ReO_4$ in blood. By clearance from the blood during the time, the perrhenate amount also decreases in stomach. This is a positive feature indicating that additional doses are not given to the other organs [32, 33].

There is no remarkable differences regarding the processes of the preparation, quality controls and general biodistribution behaviors for our produced $^{188/186}$Re-HEDP cocktail in compare of reported standalone ^{188}Re and ^{186}Re in the previous studies [11, 12, 34, 35]. Besides, by employing only the routine ^{186}Re production method and without any further experiments, we achieved the simultaneous production of two useful radiopharmaceuticals in compositional form. In addition, by applying this cocktail radiopharmaceutical and with noticing ^{188}Re and ^{186}Re complementary properties, the more efficacy can be achieved.

In the previous works the bone uptake of ^{186}Re-HEDP was indicated 20 – 30 % of the injected dose [21]. In current study, the accumulation of the radioactivity in the bone tissues with increasing trend reaches to nearly 70 % in the study time.

The biodistribution similarity of ^{188}Re and ^{186}Re in the cocktail form in different organs is clear from Figure. 4. The figure shows early bone accumulation of both radionuclides with appropriate values for the cocktail radiopharmaceutical. In addition, the charts show that the accumulation of both ^{188}Re and ^{186}Re are almost same in bone and the other organs.

Figure 4 shows that rhenium radionuclides are quickly cleared from the blood pool resulting that the other organs do not receive an additional radiation dose. In addition, no significant uptake was observed in critical organs.

Imaging results

Imaging results of the prepared radiolabeled compound show that there is conformity with the biodistribution data.

After 24 h of $^{188/186}$Re-HEDP injection, the major uptake can be seen in femurs, knees, skull and vertebral column (Figure 5). The low levels of $^{188/186}$Re-HEDP uptake in the kidneys can be seen and the accumulated activity in other organs is insignificant.

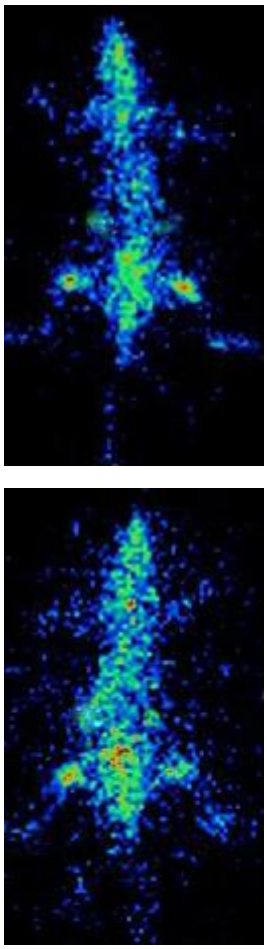

Fig 5. Planar scintigraphic images of $^{188/186}$Re-HEDP 24 h post injection in wild-type rat calibrated on gamma photons: 186 keV for ^{186}Re (above) and 155 keV for ^{188}Re (below).

CONCLUSION

The compositional radiopharmaceutical of $^{188/186}$Re-HEDP has been prepared with high purity, with no additional work for routine preparation of ^{186}Re-HEDP. The biodistribution investigation indicates that prepared cocktail of bone seeking radiopharmaceuticals with complementary features demonstrate high and durable skeletal uptake, with minimum accumulation in other vital organs. $^{188/186}$Re-HEDP preparation with simultaneous production of its constituent radioisotopes, ^{188}Re and ^{186}Re can be a useful agent to affect different sized metastatic lesions. The lower energy and longer half-life of ^{186}Re causes dose accumulation in small lesions for longer period of irradiation time, while ^{188}Re which has shorter half-life and higher energy/penetration range is a good agent to irradiate larger lesions. Our initial investigation shows promising results in rats. This compositional radiopharmaceutical can be useful agent with higher therapeutic efficiency in treatment of osseous metastatic lesions.

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