Original Article

Rhenium-188 Hydroxyethane 1,1-Diphosphonic Acid (HEDP) for Bone Pain Palliation Using BARC-HEDP Kits versus Pars-HEDP Kits: A Comparison on Preparation and Performance Aspects at Hospital Radiopharmacy

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Abstract

Purpose of the Study: Rhenium-188 hydroxyethane 1,1-diphosphonic acid (HEDP) is a clinically established radiopharmaceutical for palliation of bone pain due to osseous metastases. Recently, the Bhabha Atomic Research Centre (BARC) had developed a freeze-dried kit for the preparation of rhenium-188 HEDP. The present study compares the radiochemistry aspects of indigenous BARC-HEDP kits with commercially available HEDP kits from Pars Isotope Company, Iran. **Materials and Methods:** Freeze-dried HEDP kits were obtained from Radiopharmaceuticals Division, BARC, and Pars Isotope Company, Iran. Following recommended procedures, rhenium-188 HEDP was prepared using freeze-dried kits from both sources using freshly eluted rhenium-188 sodium perrhenate obtained from a commercial tungsten-188/rhenium-188 generator. **Results:** Both kits could be used for the preparation of rhenium-188 HEDP in >95% radiochemical purity (RCP). Rhenium-188 HEDP prepared from both kits showed comparable *in vitro* stability as well as pharmacokinetic properties. The normal bone-to-soft tissue ratio observed for rhenium-188 HEDP prepared using BARC-HEDP kit and Pars-HEDP kit was 1.993 and 1.416, respectively. **Conclusions:** Both HEDP kits provided a user-friendly solution for the preparation of rhenium-188 HEDP. While Pars-HEDP-kit permits the addition of only 2 mL of rhenium-188 perrhenate solution per kit vial, BARC-HEDP-kit allows up to 5 mL. This feature permits the preparation of patient dose of rhenium-188 HEDP even with older generators providing rhenium-188 perrhenate having a low radioactive concentration (activity/mL). In addition, availability of an indigenous product is always preferable over imported options.

Keywords: *HEDP kits, bone pain palliation, freeze-dried kits, osseous metastases, radiopharmaceuticals, rhenium-188*

Introduction

Osseous metastases are very common among patients with cancers of prostate, breast, lung, renal, and thyroid. Bone pain as a result of osseous metastases significantly compromises the quality of life of the patient. Under such conditions, the patient is often referred for palliative therapy to improve the quality of life.[1,2]

Today, bisphosphonate radiopharmaceuticals are widely used in clinical practice for palliative therapy of osseous metastases. The procedure involves selective delivery of radiation dose to the bone lesion causing the pain to the patient. This treatment, which can be repeated, is often well tolerated by the patient. Apart from phosphorus-32 (as orthophosphate),[3] which was used as early as 1932, and Food and Drug Administration approved strontium-89 chloride (Metastron™),[4,5] there are several other radiopharmaceuticals in clinical practice for the treatment of bone pain. Samarium-153 EDTMP (Quadramet®; EDTMP – ethylenediamine tetramethylene phosphonic acid),[6] rhenium-186 HEDP,[7] rhenium-188 HEDP,[8] etc., are some examples of clinically useful bone pain-palliating agents. Lutetium-177 EDTMP is one of the recent entrants to the list of clinically useful bone pain-palliating agents.[9] A recent review[10] on bone pain-palliating agents provides an excellent perspective beyond strontium-89 and samarium-153. In another review, a comparative evaluation was made between surface bone-seeking

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radiopharmaceuticals, namely rhenium-186 HEDP, rhenium-188 HEDP, samarium-153 EDTMP, and the volume-seeker strontium-89 for the treatment of skeletal metastases.[11] This study convincingly revealed that all the above radiopharmaceuticals are helpful in rendering pain relief to the patient with no significant difference in their therapeutic efficacy or toxicity.[11] In this context, the choice of a radiopharmaceutical for bone pain palliation can be made on the basis of local availability and other logistical factors.

Rhenium-188 has a significant advantage over other reactor-produced therapeutic radioisotopes such as samarium-153 and lutetium-177, since it can be obtained from a generator. Hence, in any hospital radiopharmacy housing a tungsten-188/rhenium-188 generator, rhenium-188 HEDP can be prepared and used "on demand" rather than depending on reactor-produced radioisotopes for palliative therapy. There are several reports in favor of the clinical use of rhenium-188-HEDP for bone pain palliation.[8,11,12] A recent study using rhenium-188-based multifunctional bone-seeking agent in patients with metastatic breast cancer showed encouraging results.[13]

Recently, the Bhabha Atomic Research Centre (BARC) has developed freeze-dried HEDP kits for the preparation of rhenium-188 HEDP.[14] The present study reports the comparative evaluation of BARC-HEDP kits with a commercially available freeze-dried HEDP kit from Pars Isotope Company, Iran, and the relative benefits of BARC freeze-dried kits over the commercial kits are discussed.

Materials and Methods

General

Freeze-dried HEDP kits were obtained from Radiopharmaceuticals Division, BARC, and Pars Isotope Company, Iran. Rhenium-188 as perrhenate was obtained from a commercial tungsten-188/rhenium-188 generator from the Isotope Technologies Garching, Germany. RCP of the preparation was determined using Whatman No. 3 paper chromatography (PC) strips. Radioactivity distribution on PC strips was recorded on MiniGITA γ-radioactivity thin-layer chromatography (TLC) scanner, obtained from Raytest, Germany.

Typical procedure for the preparation of rhenium-188 HEDP using freeze-dried BARC-HEDP kits

Approximately 100 μL (1 μmol) of sterile ammonium perrhenate solution (supplied with the kit) was thoroughly mixed with 1 mL of freshly eluted sodium rhenium-188 perrhenate ($Na^{188}ReO_4$) from the tungsten-188/rhenium-188 generator. This solution was aseptically added to freeze-dried BARC/Pars HEDP kit vial and the vial was heated at 100°C for 15 min. After cooling the reaction vial to room temperature, the preparation was brought to physiological pH by adding 0.5 mL of sterile 1 M sodium acetate solution (supplied with the kit).

BARC-HEDP kits can be used for the preparation of rhenium-188 HEDP using up to 5 mL of rhenium-188 activity with minor modification to the procedure. For every milliliter of rhenium-188 activity, 100 μL (1 μmol) of sterile ammonium perrhenate (supplied with the kit) was added and the solution was aseptically transferred to freeze-dried BARC-HEDP kit vial. Subsequently, the kit vial was heated at 100°C in a water bath. Incubation time was set according to the volume of the activity added to the BARC-HEDP kit vial [Table 1]. After cooling the reaction vial to room temperature, the preparation was brought to physiological pH by adding 0.5 mL of sterile 1 M sodium acetate solution (supplied with the kit).

Preparation of rhenium-188 HEDP using freeze-dried Pars-HEDP kit

Preparation of rhenium-188 HEDP using Pars-HEDP kit was carried out following the procedure suggested by the manufacturer. About 1–2 mL of freshly eluted rhenium-188 activity was added to kit vial 1 containing potassium perrhenate. Vial 2 was reconstituted with sterile saline (1 mL) and the resulting solution was transferred to vial 1. Subsequently, vial 1 was heated at 100°C for 30 min. After cooling the reaction vial to room temperature, sodium acetate buffer from vial 3 was added to bring the solution to physiological pH.

Determination of RCP of rhenium-188 HEDP

RCP of rhenium-188 HEDP complex was determined by PC using a two-solvent system, namely acetone and physiological saline. Two PC strips (11.5 cm long) were prepared by spotting ~4 μL of the test solution. One of the strips was developed in acetone, while the other was developed in physiological saline. In acetone, rhenium-188 HEDP complex and reduced rhenium (ReO_2) remain at the point of spotting, while perrhenate moves to the solvent front. In saline, both rhenium-188 HEDP and perrhenate move to the solvent front, while reduced rhenium remains at the point of spotting. Developed strips were analyzed on a TLC scanner and, from the peak area measurements, RCP of rhenium-188 HEDP complex was calculated.

Table 1: Parameters for efficient preparation of rhenium-188 HEDP using BARC-HEDP kit

Volume of activity (mL)	Volume of NH_4ReO_4 solution (μL)	Volume of sodium acetate solution (μL)	Incubation time at 100°C (min)
1	100	500	20
2	200	500	20
3	300	500	30
4	400	500	60
5	500	500	60

Results and Discussion

An important consideration in any hospital radiopharmacy having a commercial tungsten-188/rhenium-188 generator is to make the best use of rhenium-188 activity available from it. This is important for economically sustaining the rhenium-188-based therapy services in the hospital as it involves high initial cost of tungsten-188/rhenium-188 generator.

Rhenium-188 HEDP is an effective bone pain-palliating agent with proven clinical record. From the hospital radiopharmacy point of view, rhenium-188 HEDP has a significant advantage over other pain-palliating agents based on reactor-produced radioisotopes. This radiopharmaceutical can be prepared "on demand" and qualified patients can receive palliative therapy immediately. Freeze-dried kits offer an easy route for the preparation of radiopharmaceuticals. Since we had received freeze-dried kits from two sources, namely BARC, India, and Pars Isotope Company, Iran, we decided to compare the kits to evaluate their characteristics and performance.

HEDP kits obtained from both sources (BARC and Pars Isotope) were three-vial kits [Table 2]. Both methods used carrier rhenium for the preparation of rhenium-188 HEDP. While the recommended maximum volume of activity in Pars-HEDP kit was 1–2 mL, BARC-HEDP kit offered flexibility of up to 5 mL of rhenium-188 activity. Similarly, for the preparation of rhenium-188 HEDP, Pars-HEDP kit required incubation at 100°C for 30 min, while the incubation time at 100°C for BARC-HEDP kits varied with the volume of activity added to the HEDP vial [Table 1]. Upon reconstitution of the freeze-dried HEDP kit vial following the recommended procedure, rhenium-188 HEDP could be prepared with >98% RCP by both methods. Typical PC patterns obtained with rhenium-188 HEDP in acetone and saline are shown in Figure 1. Physicochemical characteristics of rhenium-188 HEDP prepared using BARC-HEDP kit as well as Pars-HEDP kit remained similar [Table 2]. Typical clinical images obtained with rhenium-188 HEDP prepared from BARC-HEDP kits and Pars-HEDP kits are shown in Figure 2. No observable differences in pharmacokinetics of rhenium-188 HEDP prepared from the two different kits could be observed.

BARC-HEDP kits offer a flexibility to use rhenium-188 activity up to 5 mL. This flexibility is advantageous at the near end of the life of the tungsten-188/rhenium-188 generator when radioactive concentration (RAC) of the eluate is low. Under such circumstances, it may still be possible to prepare a patient dose of rhenium-188 HEDP using a single BARC-HEDP kit rather than using multiple Pars-HEDP kits for patient dose preparation.

Conclusions

A comparative evaluation of freeze-dried HEDP kits from two sources, namely BARC, Mumbai, and Pars Isotope Company,

Table 2: A comparison between BARC-HEDP kits and Pars-HEDP kits

Parameter	BARC-HEDP kit	Pars-HEDP kit
Vials in kit	3	3
Use of carrier rhenium	Yes	Yes
Maximum volume of rhenium-188 activity	5 mL	2 mL
Incubation temperature	100°C	100°C
Incubation time	Depends on the volume of activity added [Table 1]	30 min
Quality control parameters of rhenium-188 HEDP		
Appearance	Clear	Clear
Color	Pale yellow - amber	Pale yellow - amber
pH	5-6	5-6
Radiochemical purity (PC)	>98%	>98%

BARC=Bhabha Atomic Research Centre, HEDP=Hydroxyethane 1,1-diphosphonic acid, PC=Paper chromatography

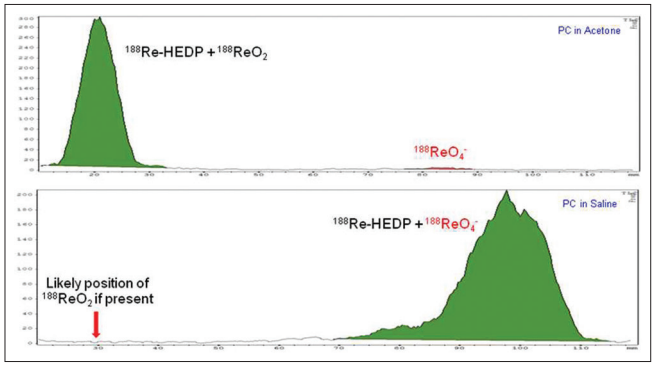

Figure 1: Typical paper chromatography pattern of rhenium-188 hydroxyethane 1,1-diphosphonic acid in acetone and physiological saline

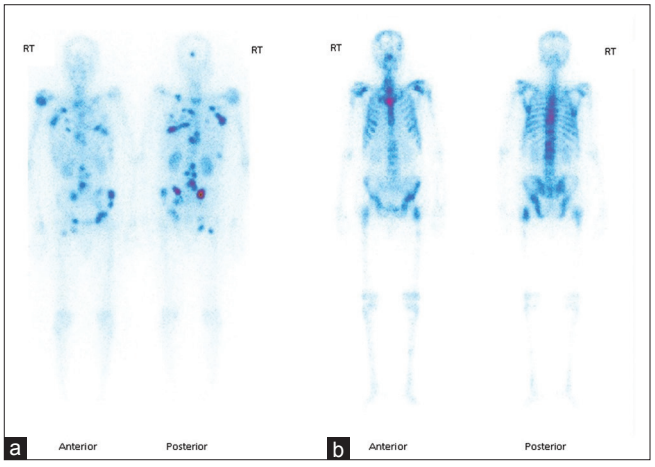

Figure 2: Clinical images of patients administered with rhenium-188 hydroxyethane 1,1-diphosphonic acid prepared using (a) freeze-dried BARC-HEDP kits and (b) freeze-dried Pars-HEDP kits at 24-h post-injection. The normal bone-to-soft tissue ratio was 1.993 and 1.416, respectively, for rhenium-188 HEDP prepared using BARC-HEDP kit and Pars-HEDP kit

Iran, showed similarity in terms of ease of preparation, quality control, physicochemical parameters, and *in vivo* pharmacokinetics. However, BARC-HEDP kit offered certain advantages such as its local availability, lower-cost, and most importantly the flexibility to use up to 5 mL of rhenium-188 activity. This would help in the preparation of patient dose of rhenium-188 HEDP even with eluate of low RAC.

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Conflicts of interest

There are no conflicts of interest.

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