PRELIMINARY STUDIES TO OBTAIN ^{186}Re-PERRHENATE. BIOLOGICAL PATTERN IN RATS AND LABELLED COMPOUNDS

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ABSTRACT

^{186}Re is an important radionuclide to be used for palliative therapy of bone pain associated with skeletal metastases. ^{186}Re is employed in Nuclear Medicine complexed with molecules such as EHDP (ethane-1-hydroxy-1-1-diphosphonate) and MDP (methylene diphosphonate). Samples of natural metallic rhenium were irradiated inside quartz ampoules under a thermal neutron flux of 1 X 10^{13} n.cm^{-2}.s^{-1} during 3 hours; the ^{186} Re activities produced was about 1110 MBq with a specific activity of about 37 MBq ^{186}Re/mg Re. The preparation of ^{186}Re-perrhenate from metallic ^{186}Re was achieved by the oxidation of Re with H_2O_2 and further neutralization with aqueous ammonia. The solution was sterelized by filtration with 0.22 μm millipore filters. The biodistribution of ^{186}Re-perrhenate was studied in rats at the 2, 4, 6, 24 and 48 hours time-points and the same biological pattern as for $Na^{99m}TcO_4$ was observed without any uptake in other organ.

INTRODUCTION

Several radiotracers or their labelled compounds have been used to palliative extreme skeletal pain caused by disseminated bone metastases for many years, but none has achieved widespread clinical application. Rhenium is a beta emitter with excellent physical properties that may be useful for the formulation of radiotherapeutic agents: (a) half-life: 90.64 hours; (b) main emissions: β^- particles, E = 1.073 MeV (73%) and 0.9494 MeV (21.0%) with a range in tissue of the order of 4.5 mm and 3.8 mm, respectively; (c) emission of photon with an ideal energy of 137 KeV (9%) which can be used to image; (d) it is produced in nuclear reactor with activities ranging from a few millicuries to tens of millicuries [1].

Rhenium-186 as ^{186}Re-perrhenate form can be used for the preparation of ^{186}Re complexes by the tin-reduction method. It is applied in nuclear medicine complexed with molecules such as MDP (methylene diphosphonate) and EHDP (ethane-1-hydroxy-1,1-diphosphonate). Additionally the rather low specific activities of these preparations reduce their nuclear medical value.

In the present work, the experimental studies about the irradiation conditions of metallic rhenium and ^{186}Re-perrhenate preparation were started. A biological pattern of ^{186}Re-perrhenate in rats was also studied. The obtained ^{186}Re product was used to label MDP and then a biodistribution in rats was performed, after i.v. administration.

MATERIALS AND METHODS

Mettalic rhenium-186 was purchased from Fluka Chemie AG and methylene diphosphonic acid (MDP) was obtained from Plenum, USA, both with analytical degree.

1. Irradiations: Samples of natural metallic rhenium were irradiated inside quartz ampoules in the reactor IEA-R1 at IPEN-CNEN/São Paulo using a thermal neutron flux of 1×10^{13} n.cm^{-2}.s^{-1}, during 8 hours. After that, the samples were left to cool for a period of 5 days to reduce ^{188}Re content. The obtained ^{186}Re specific activity was about 37 MBq ^{186}Re/mg Re.

2. Preparation of ^{186}Re-perrhenate: The preparation of ^{186}Re-perrhenate from metallic rhenium-186 was achieved by the oxidation of ^{186}Re with H_2O_2 and further neutralization with aqueous ammonia.

3. Preparation of ^{186}Re-MDP complex: The preparation was performed by the reduction method [2]. 8.7mg of $SnCl_2.2H_2O$ was added in 1.0ml of HCl 0.04N previously purged nitrogen, 1.0 ml of this solution was added in 32.4mg of MDP. The pH of this solution was adjusted 1.4 with NaOH 0.2N. The solution was sterilized by filtration with millipore filter of 0.22 μm, proved to be necessary since $SnCl_2.2H_2O$ partially forms an insoluble precipitate upon dissolution in aqueous media. 300 μl of MDP-Sn were added in 100 μl of $NH_4^{186}ReO_4$ (621.6MBq/ml-138.8mg/ml) in a evacuated and sealed vial and allowed to react at temperature for 30 minutes. The isolation of the ^{186}Re-MDP complex was performed by liquid chromatography on a Sephadex LH 20 support. The pH of the eluting HCl solution was 3.8. The radioactivity was measured in a counter (ANSR_ABBOT).

4. Absorbance measurements in the UV-VIS region: The complex was submitted to absorbance measurements at UV-VIS spectrophotometer, INTRALAB, DMS 80, with 10 mm quartz cells, path lenght , 30 and 90 minutes after reaction, to check its stability.

5. Biodistribution studies: Biodistribution was performed in rats with one pad with lesion in tibia and with the other pad normal for control, after i.v. administration of the complex ^{186}Re-MDP. The animals were sacrified after 180 minutes and the uptake of blood samples and some organs was determined. Biological behavior of ^{186}Re-perrehenate was also performed in rats after 2 ,4 , 6, 24, and 48 hours of the dose administration.

RESULTS AND DISCUSSION

In our experiments the obtained specific activities of Re-186 were too low. As a result, the radioisotope is only suitable for researches. For medical purposes, it is necessary to have higher neutron fluxes (at least 5×10^{13}n.cm^{-2}.s^{-1}) and longer irradiation periods (2 - 5 days).

The results of the preliminary studies of biological distribution in rats (Table 1) showed the rapid renal clearance of the complex ^{186}Re-MDP. The ratio between both uptakes, in the lesion bone and in the normal bone was 2. This, and the other organs uptake were above what we expected. Maybe this is due to the instability of the complex in vivo and in vitro.

The biological behavior of ^{186}Re-perrhenate (Table 2) showed the same biologial pattern of $Na^{99m}TcO_4$ without any uptake in any organ. This is an advantage in terms of dosimetry of radiation for the patients.

The wavelengths corresponding to the maximal absorbance of the ^{186}Re-MDP complex, 30 and 90 minutes after reaction were respectively, 436 and 351 nm.

The observed displacement for λ_{max} suggests the chemical instability of the complex.

Further studies will be carried out in order to optimize the conditions for the target irradiation and for the compound labelling.

TABLE 1 - Percent injected dose of ^{186}Re-MDP/organ 180 minutes after i.v. administration

ORGANS	% DOSE / ORGAN
Liver	4.37 ± 0.83
Kidneys	2.33 ± 0.09
Lungs	0.22 ± 0.09
Intestines	0.24 ± 0.09
Stomach	1.05 ± 0.75
Muscle	0.02 ± 0.01
Heart	0.07 ± 0.03
Lesion Bone	0.70 ± 0.03
Normal Bone	0.34 ± 0.02
Blood	0.24 ± 0.08

TABLE 2 - Biological distribution of $Na^{186}ReO_4^-$ in rats - percent injected dose/organ

ORGANS	TIME AFTER DOSE ADMINISTRATION (HOURS)				
	2	4	6	24	48
Kidney	0.77 ± 0.20	0.65 ± 0.28	026 ± 0.07	0.04 ± 0.05	0.00
Liver	1.20 ± 0.20	0.69 ± 0.49	0.72 ± 0.17	0.06 ± 0.05	0.003 ± 0.006
Heart	0.09 ± 0.02	0.25 ± 0.34	0.05 ± 0.01	0.01 ± 0.01	0.00
Spleen	0.07 ± 0.006	0.05 ± 0.006	0.03 ± 0.01	0.003 ± 0.006	0.00
Stomach	3.07 ± 0.60	1.42 ± 0.13	0.94 ± 0.32	0.24 ± 0.29	0.01 ± 0.01
Thyroid	0.17 ± 0.05	0.18 ± 0.07	0.14 ± 0.03	0.03 ± 0.03	0.00
Bone	0.08 ± 0.03	0.06 ± 0.03	0.06 ± 0.03	0.01 ± 0.01	0.00
Muscle	0.03 ± 0.006	0.03 ± 0.02	0.02 ± 0.01	0.003 ± 0.006	0.00
Saliv.Gland	0.03 ± 0.01	0.02 ± 0.006	0.001 ± 0.00	0.003 ± 0.006	0.00
Lymp.Gland	0.13 ± 0.03	0.07 ± 0.05	0.07 ± 0.03	0.006 ± 0.011	0.00
Lungs	0.24 ± 0.01	0.16 ± 0.03	0.11 ± 0.04	0.02 ± 0.01	0.00

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