^{153}Sm-EDTMP. PHASE II: STUDIES FOR A ROUTINE PRODUCTION

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ABSTRACT

^{153}Sm-EDTMP is used in Nuclear Medicine as a radiotherapeutic agent in the treatment of metastatic bone cancer pain. ^{153}Sm was obtained by neutron irradiation of enriched samarium (^{152}Sm, 98.7%) in IEA-R1 reactor of IPEN-CNEN/SP, using thermal flux of 1.5 X 10^{13} n/cm^2. sec. during 14.5 hours (periods of 7 and 7.5 hours) and 48 hours (continuously). The activities obtained were 52.2 and 143 mCi (1.93 - 5.29 GBq), respectively, at the end of irradiation. ^{153}Sm Cl_3, 35 - 45 mCi (1.30 - 1.67 Gbq) was added into lyophilized kits containing 50 mg of EDTMP (ethylenediaminetetramethylene phosphonate) pH = 10.5, and adjusted to pH 7.5 - 8.0 with 0.5M buffer phosphate at final volume 1.7 - 2.0 ml. Radiochemical purity was determined by paper chromatography, the complexation yield was higher than 95 %; the complex remained stable during 5 days at room temperature. Microbiological control and pyrogen test were evaluated in all samples, showing the sterility and non-pirogenicity of ^{153}Sm-EDTMP. Biodistribution was performed in female rabbit (5.5 Kg) in a gamma-camera at 1, 3, and 6 hours after i. v. dose 2.4 mCi (88.8 MBq). A selective and higher osseous uptake was observed, with rapid blood clearance and fast urinary elimination.

INTRODUCTION

Samarium-153 and other rare earth radionuclides have been proposed as potential radiotherapeutic and diagnostic skeletal imaging agents. The more favorable physical characteristics of Samarium-153 (^{153}Sm): half-life 46.27 hours, beta emitter 810 keV (20%), 710 (50%) and 640 (30%), gamma emission 103 keV (29%) which is suitable for conventional scintigraphy, permits optimum internal radiotherapy with prospective estimation of radiation dose to metastases and bone marrow in each patient. The short half life allows for efficient handling and the possibility of fractionated dosing. The average penetration range of the beta particle is 0.83 mm in water. These radionuclides are labeled with phosphonates which preferably localize in active bone, and specially in sites of metastases.

Early data indicate that ^{153}Sm-EDTMP may be considered effective agent to treat metastatic bone cancer in human. Courvin et. al (1986) have demonstrated the efficacy as a therapeutic radiopharmaceutical in dogs with spontaneous bone cancer.[1]

Goeckeler et. al. (1987) have produced a series of stable complexes of ^{153}Sm using multidentate acetate and phosphonate ligands demonstrating the highest skeletal uptake and lowest blood and nonosseous tissue activity of ^{153}Sm- EDTMP in rats.[2]

Turner et. al. (1989) measured skeletal uptake of ^{153}Sm-EDTMP in 35 patients and found a range of 40 % - 95 % of injected dose (%ID), pain was relieved in 65 % of patients for periods ranging from 4 to 35 weeks, following a single dose administrated.[3].

Holmes (1992) reported the study of ^{153}Sm-EDTMP in animals. The results of biodistribution showed 50 - 66 % bone uptake within 2 - 3 hours and additional 33 - 50 % of the complexed is excreted in the urine within 8 hours after injection.[4]

Farhanghi (1992) administered escalating amounts of ^{153}Sm-EDTMP, from 0.1 to 1.0 mCi / kg (3.7 - 37 MBq / kg), in 22 patients with painful metastatic bone cancer. Pain palliation occurred in 65 % of the treated patients, thrombocytopenia was manifested in patients who had low pretreatment platelet counts. Toxicity, defined as bone marrow suppresion, was mild and transient.[5]

Bayouth et. al.(1994) evaluated the dosimetry and toxicidy of ^{153}Sm-EDTMP in 19 patients, who had received up to four injections of 18.5 MBq (0.5 mCi) or 37 MBq (1 mCi) / kg of body weight. Skeletal retention was calculated from urinary excretion. Thirteen patients (68%) reported significant pain relief from this radionuclide therapy with limited red marrow doses and no toxic effects in other organs. [6]

The aim of this work was to determine the parameters for ^{153}Sm-EDTMP preparation, the irradiation conditions, the labelling and the quality control methods for routine production adaptability.

MATERIALS AND METHODS

1- Irradiation: The Sm-153 was obtained by neutron irradiation of enriched Samarium (^{152}Sm, 98.7 %) (nitrate form) in IEA-R1 reactor of IPEN - CNEN / SP using a thermal flux 1.3 - 1.5 x 10 ^{13} n / cm ^{2} sec. during two periods of time: 1) 14.5 hours (periods of 7 - 7.5 hours a day) and 2) 48 hours, continuously. The enriched Samarium was dissolved stoichiometrically in 1N HNO_3 to 10 mg / ml with water, from this stock solution 1 - 5 mg of Sm was placed into a quartz vial and dried. The quartz vial was flame sealed and encapsulated in an aluminium can. Following the irradiation time and, after 16 or 18 hours the target was opened and then dissolved in 2 - 3 ml 0.1N HCl at 80 - 90° C, in a concentration of

aproximately 1 mg Sm / ml, determining the total activity. This solution was filtered through a Millipore filter (0.22 μ).

2- Kit formulation: The EDTMP kit in lyophilized form was prepared at pH 10.5, containing 50 mg EDTMP, from ICN-Biochemicals, per vial. The product was lyophilized in "Interfrigo" equipment at 0° C during 24 hours and, kept at 4° C for stability evaluation.

3- Labelling procedure: A solution of ^{153}Sm in 0.1 N HCl, 35 - 45 mCi (1.30 - 1.67 GBq) / ml was added to a lyophilized EDTMP kit, the volume was adjusted with 0.3 ml 0.1N HCl and 0.5 ml 0.05 M phosphate buffer with a final pH 7.5 - 8.0 at the molar ratio EDTMP / Sm 26 - 40. Final volume was 1.7 - 2.0 ml.

4 -Radiochemical control: The radiochemical purity was assayed by Whatmann 3MM paper chromatographic system (1 x 10cm) in NH_4OH:MeOH:H_2O (0.2:2:4) v/v/v as a solvent with Rf = 1.0 (^{153}Sm-EDTMP) and Rf= 0.0 ($^{153}SmCl_3$) in this system.

5- Biological Control: Microorganisms (aerobic, anaerobic, fungus and yeast) were determined in several cultures medium: Thioglicolate (Merck), Tryptone Soya Broth (Oxoid) and Sabouraud Broth 2 % glucose (Merck) at room temperature and 37°C during 10 days. Pyrogen (a fever-producing bioproduct of gram-negative bacteria) was evaluated by LAL test (Limulus Amaebocyte Lysate reagent) which is the most sensitive and specific means to detect pyrogen at 37°C in 1 hour.

6- Biodistribution: The biological distribution of ^{153}Sm-EDTMP was studied in female rabbit (5kg) 1, 3 and 6 hours after i.v. dose of 2.4 mCi (88.8MBq) / 0.2 ml in a gamma camera GE - STAR CAM Mod 600 XR/T with a computer GE Mod 4000.

RESULTS

Table 1 presents the results of irradiation of Samarium oxide (enrichment, 98.7%) in IEA-R1 reactor using thermal flux 1.5 x 10^{13} n/cm_2 sec. The activities obtained from 1 mg ^{152}Sm (enrichment) were 52.2 - 154 mCi (1.93 and 5.70 GBq) after 14.46 and 48 hours, respectively (Table 1). Higher activities were obtained after 48 hours continuously from 2 and 5 mg of ^{152}Sm; 307 - 676 mCi (11.36 - 25.01 GBq).The ^{153}Sm obtained after 14.46 hours of irradiation was labelled with EDTMP kit and used in the biological study in rabbit: the complex is stable until 5 days (Table 2) with yield of 98.71; 97.52 and 97.25 % at 0.5, 24 and 120 hours after labelling, respectively.

Microbiological control and pyrogen test evaluated in all samples, showed the sterility and non-pyrogenicity of ^{153}Sm-EDTMP process.

TABLE 1 - Irradiation of ^{152}Sm oxide

Sm Mass (mg)	Time (hours)	Activitiy per mg	Activity (GBq) obtained	Theoretic value (%)
1.0	7.83 6.63	1.92	1.92	88.2
1.0	7.83 6.63	1.96	1.96	89.1
1.0	48	5.29	5.29	80.3
1.0	48	5.70	5.70	86.5
2.0	48	5.68	11.36	86.2
5.0	48	5.00	25.01	76.2

TABLE 2- Labelling yield (%) of radiochemical purity of ^{153}Sm-EDTMP

TIME (hours)		
0.5	24	120
98.71	97.52	97.25
98.05	96.35	95.45
97.85	97.53	96.65
97.65	96.41	96.25

Figure 1 shows the scintigrams obtained after 1, 3 and 6 hours i.v. dose of 2.4 mCi (88.8 MBq) /0.2ml of ^{153}Sm-EDTMP in rabbit, a selective and higher skeletal uptake was detected with rapid blood clearance and fast urinary excretion; hepatic uptake was not observed.

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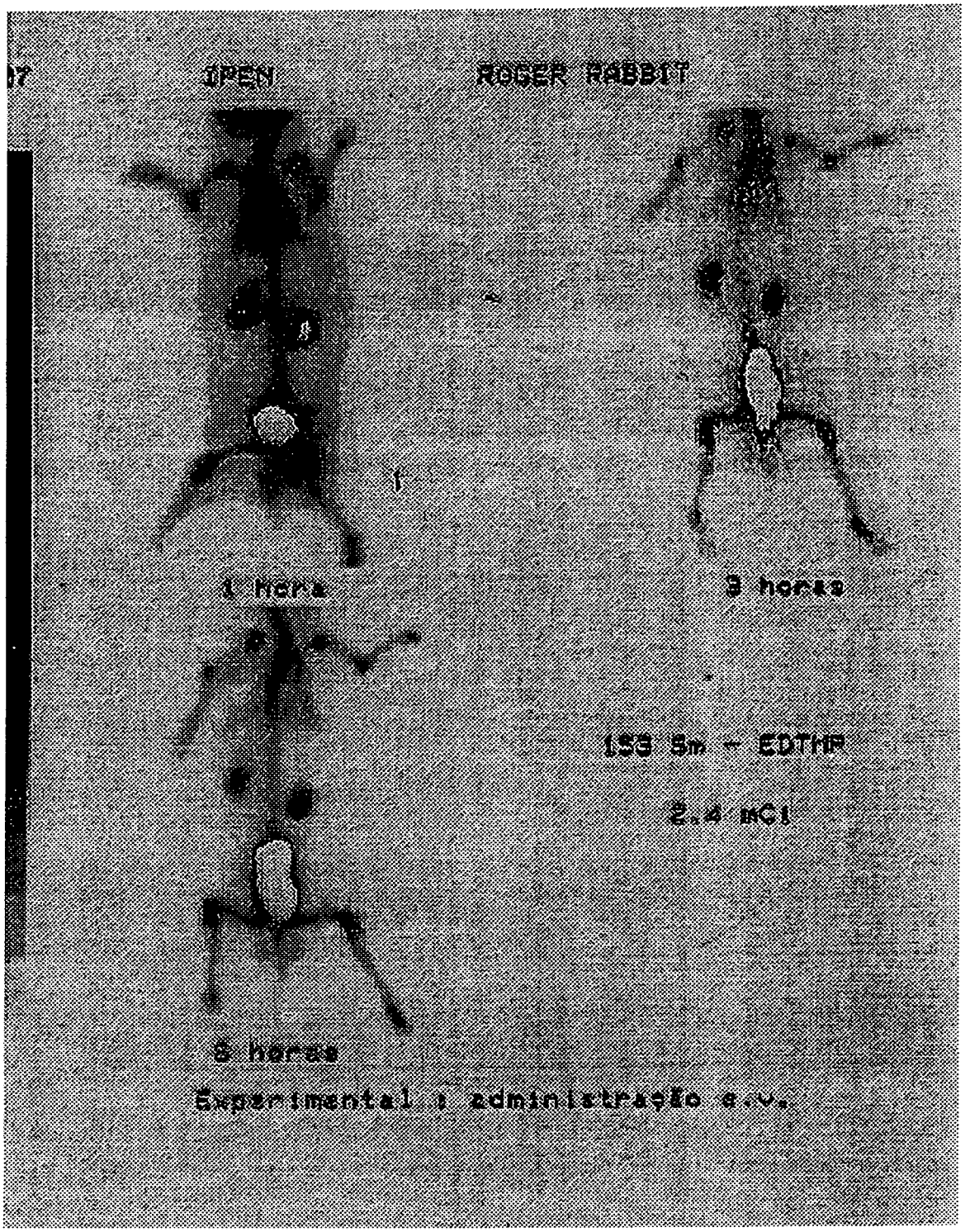

FIGURE 1 - Biological distribution of ^{153}Sm-EDTMP in rabbit