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Radiochemical and biological studies, including in non-human primates, towards indigenous development of ^{153}Sm-EDTMP

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Introduction

The combination of ease of formulation and superior biological features of ^{153}Sm-EDTMP in terms of safety and efficacy for metastatic bone pain palliation, together with the prospect of relatively reasonable cost, has prompted extensive efforts by many groups world over to standardise methods for its preparation and evaluation [1,2]. Our efforts have been directed towards establishing feasibility of use of inexpensive and freely available natural samarium oxide targets by neutron activation in medium flux reactors in our country. Towards this aim, we have formulated a number of batches of ^{153}Sm-EDTMP and evaluated the product for its ease of production, purity, stability, safety and efficacy of bone uptake and excretory pattern in test animals, including in monkeys.

Results and discussion

5-10 mg of natural samarium oxide was irradiated at a neutron flux of 6-8 x 10^{13} n. cm^{-2}. s^{-1} in the Dhruva reactor for about seven days and dissolved in hydrochloric acid. Specific activity of 500-700 mCi ^{153}Sm per mg Sm (at EOB) and radioactive concentration of over 400mCi/ml was obtained. Complexation of the samarium with a gift sample of EDTMP as well as an in-house synthesised product was carried out under conditions previously standardised by us [3] at a ligand to metal mole ratio of 20 - 40 : 1. Formulations at radioactive concentration of 10-50 mCi/ml were prepared and the radiochemical purity and stability evaluated by paper chromatography. Stability of ^{153}Sm-EDTMP in serum was also followed. The product even when stored at room temperature (RT) was found to be stable for 8 days at RC purity >98% for formulations at 10-12 mCi/ml radioactive concentration; but, as expected, formulations at much higher radioactive concentration were found to be stable for 5 days only (at RT) at a RC purity of upto 90%. High resolution γ spectrometry studies using HPGe detector revealed radio-europium contamination ($^{154/155/156}$Eu). At 2 days from EOB each mCi of ^{153}Sm contained typically 0.013 uCi^{154}Eu, 0.15 uCi ^{155}Eu & 1.5 uCi ^{156}Eu. These values are consistent with our earlier reports in literature [3,4]. Improvement of radionuclidic purity (but at the cost of reduced yield) could be achieved by radiochemical purification [4], but is not deemed essential in the context of therapeutic application envisaged and known similarity in biological behaviour of Sm and Eu chelate of phosphonates. Further, mice administered EDTMP doses of upto 4 mg / animal exhibited no untoward toxic symptoms giving a safety factor of >300 at expected adult doses. In other words, samarium content and radionuclidic purity aspects need not be deterrent factors for the use of natural samarium target for the manufacture of ^{153}Sm-EDTMP.

The bio-distribution studies in rats showed 2.5 to 3.5 % injected dose in femurs 1h p.i. for all samples and even at 5 days post formulation. Anaesthetised monkeys were administered 0.5-1 mCi 153Sm per kg through a leg vein and images recorded with a gamma camera (Siemens, Orbiter) upto 116 hours p.i. Fig.1 shows the good retention in skeleton throughout the period of study and no significant retention in any other tissues. Comparative studies using enriched 152Sm target and also a commercial sample of 153Sm-EDTMP are underway. These

results have thus established satisfactory feasibility for production, adequate safety and bio-localisation of the indigenous product so as to warrant clinical trials in patients.

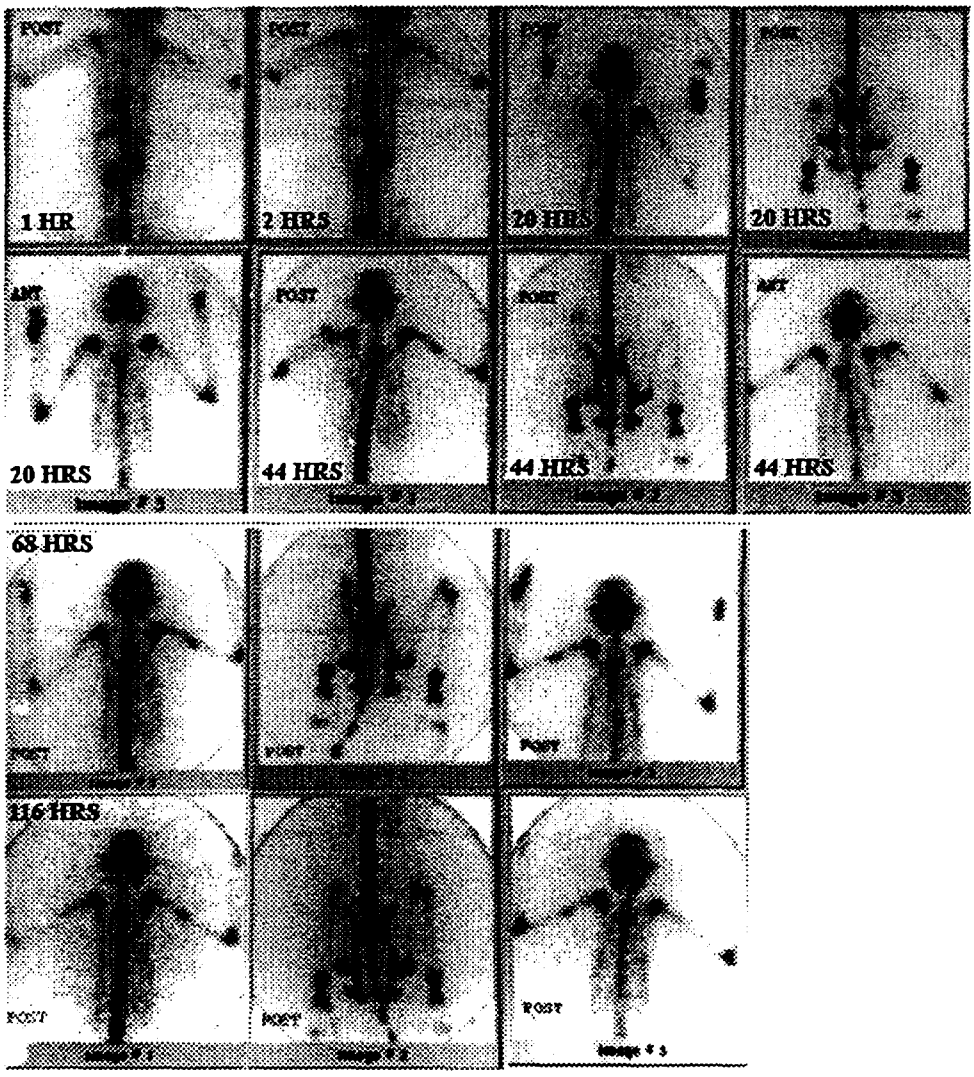

Fig. 1. Gamma camera images of a monkey injected with ^{153}Sm-EDTMP

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