Preparation and bio-distribution of ^{153}Sm-HEDTMP as a radiopharmaceutical for bone metastases

JIANG Shu-Bin,[1] LUO Shun-Zhong,[1] HU Shu,[2] DENG Hou-Fu,[2] BIN Wen-Zeng,[1] WANG Wen-Jin,[1] WEI Hong-Yuan,[1] LEI Yong[2]

([1]Institute of Nuclear Physics and Chemistry, the China Academy of Engineering Physics, Mianyang 621900;

[2]Department of Nuclear Medicine of First University Hospital, West China Medicine Center, Sichuan University, Chengdu 610041)

Abstract HEDTMP (N-(2-hydroxyethyl) ethlenediamine-1,1,2-tri(methylene phosphonic acid)) was labeled with ^{153}Sm. The formation condition, stability, rabbit bone imaging and mouse bio-distribution of ^{153}Sm -HEDTMP were investigated. The results showed that weak basic media and high ligand's concentration were favorable to form ^{153}Sm-HEDTMP, and neutral or weak basic media increase the stability of ^{153}Sm-HEDTMP. And the higher the concentration of HEDTMP was, the more stable the labeling complex was. Bio-distribution study indicated the uptake of ^{153}Sm-HEDTMP in skeleton was high ((25.68±1.22)ID%/g bone at 3 h post injection and (16.56±1.01)ID%/g bone at 48 h post injection), while the non-target tissue uptake and retention were relatively low, so ^{153}Sm-HEDTMP is a promising bone tumor therapeutic agent.

Keywords Samarium-153, HEDTMP, Bone tumor, Bio-distribution

CLC Numbers R979, R817, O628

1 Introduction

Metastases to skeleton from prostate, breast, and lung cancer are frequent in clinical practice. The palliation of patients with extreme pain of bone metastases was of primary importance in clinical management of patients with advanced cancer. Based on concentration at sites of increased bone turnover, radio-therapeutics was an effective alternative to conventional therapies. ^{153}Sm-EDTMP (ethylene diamine tetramethylene phosphonate) has been developed to palliate successfully extreme skeletal pain caused by bony metastases for many years,[1-3] although the mechanism of pain relief remained controversial.[4-6] Ligand EDTMP has been developed from EDTA (ethylene diamine tetraacetic acid), for Ref. [7] showed that ^{153}Sm coupled with HEDTA (N-(2-hydroxyethyl) ethlenediamine-1,1,2-triacetic acid), an analog of EDTA, displays more excellent biologic characteristics than ^{153}Sm-EDTA. Then, how did ^{153}Sm couple with HEDTMP, the analog of EDTMP? In this paper, we will describe the synthesis of HEDTMP and its labeling with ^{153}Sm to evaluate the feasibility as a bone tumor radiopharmaceutical.

2 Experimental

2.1 Materials

HEDTMP was synthesized in our laboratory and IR, NMR and element analysis were carried out for confirmation.

Samarium chloride solution (containing 370 MBq ^{153}Sm/mL) was prepared by irradiating natural samarium oxide in the research reactor of our institute and dissolving the irradiated target (3 GBq/g Sm_2O_3) with diluted hydrogen chloride.

The other chemical agents, all were of analytic purity, were purchased commercially and not purified before use.

2.2 Preparation of ^{153}Sm-HEDTMP

To a vial containing HEDTMP aqueous solution, $^{153}SmCl_3$ aqueous solution was added, and then the pH of solution was adjusted to a certain value. After sealing, the mixture was reacted for 30 min at room temperature (~20 °C). The radio-chemical purity of

Supported by CAEP Foundation (20020537)

Received date: 2002-07-08

^{153}Sm-HEDTMP was measured using radiopaper chromatography and the developing agent consisted of pyridine: ethanol: water (1:2:4 *V*/*V*). The R_f values of free $^{153}Sm^{3+}$ and ^{153}Sm-HEDTMP were 0 and 0.7, respectively.

2.3 Stability of ^{153}Sm-HEDTMP

The pH value of ^{153}Sm-HEDTMP solution obtained under optimum condition was changed to physiologic value and then the percent complexation of ^{153}Sm-HEDTMP was examined at different time intervals with the method mentioned above.

2.4 Rabbit imaging

About 74 MBq of ^{153}Sm-HEDTMP in ~0.5 mL was injected through the ear vein of a New Zealand rabbit weighting 2 kg, and the rabbit was imaged by a SPECT instrument, provided by Elscint Israel, at 24 h post-injection.

2.5 Bio-distribution

Bio-distribution study was performed in Kunming mice weighing (18±2) g. 18.5 kBq of ^{153}Sm-HEDTMP in ~0.2 mL was injected through tail vein, and the mice were sacrificed at specific time intervals by cervical dislocation. The tissues and organs were excised, weighed and counted over a NaI(Tl) scintillation detector. For skeletal uptake studies, femur bone was chosen. The distribution of activity in different organs was calculated as percent injected dose per gram (%ID/g).

3 Results and discussion

3.1 Influence of pH value on ^{153}Sm-HEDTMP formation

Fig.1 implies that HEDTMP is the analog of EDTMP and it has at least 6 protonation sites, corresponding to three phosphonate groups, three further sites existing in principle on the central amine groups and a hydroxyethyl group. Therefore HEDTMP could couple Sm^{3+} and the factors affecting formation of ^{153}Sm-HEDTMP must be similar to those in the formation of ^{153}Sm-EDTMP which could be easily prepared at pH 8~10.[1] Fig.2 showed that the influence of pH value on the complex formation was similar to the formation of ^{153}Sm-EDTMP: when the magnitude of ligand was 4 mg, the pH range, in which a satisfied labeling yield could reach, was 8~10, whereas the pH value range was 6.5~11.5 when ligand was 10 mg. Sm-complexes were unstable because of their hydrolysis, especially in strong basic media solution. But it was also unfavorable to the formation in strong acid media (Fig.2), partially because the ligand could not dissociate its H^+ and form anion. Therefore, the pH value used in the late experiments was fixed at 8~10. Increase of ligand quantity can widen the pH range in which satisfied labeling yield can be gotten, and influence of the magnitude of ligand was examined, as shown in Fig.3.

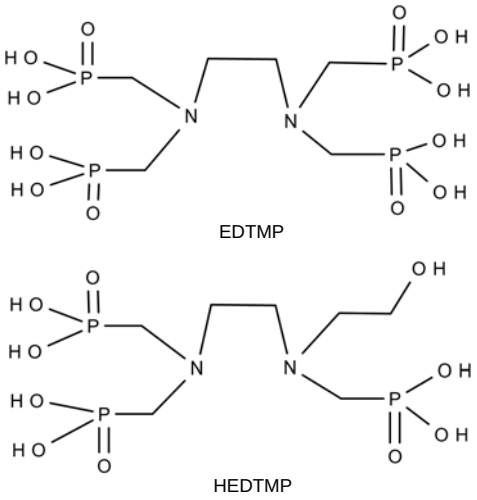

Fig.1 The molecular structure of EDTMP and HEDTMP.

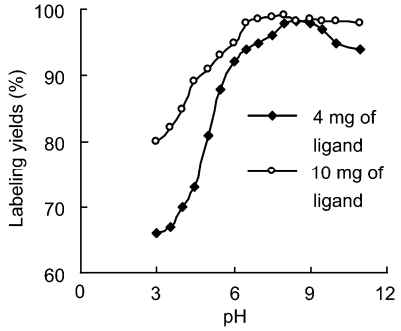

Fig.2 Effect of pH on yields.

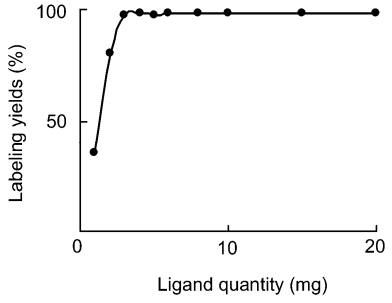

Fig.3 Effect of ligand on yield (pH8).

3.2 Influence of ligand on ^{153}Sm-HEDTMP formation

Fig.3 suggested that the labeling efficiency increased with amount of HEDTMP when HEDTMP was less than 3 mg, and the labeling efficiency reached 97% when ligand was 3 mg. It was necessary to increase ligand concentration for preventing ^{153}Sm-EDTMP from dissociation, which could cause higher non-target uptake in vivo,[8] but our work hinted that excessive ligand would reduce the bone uptake due to the competitive adsorption of ^{153}Sm-EDTMP and dissociative EDTMP ligand on bone.[9] Considering these facts, ^{153}Sm-EDTMP was prepared at pH 8~10 and 4 mg of HEDTMP was chosen.

3.3 Stability of ^{153}Sm-HEDTMP in vitro

Fig.4 indicated that ^{153}Sm-HEDTMP exhibited high stability in vitro, which was similar to ^{153}Sm-EDTMP, and the percentage complexation of ^{153}Sm-HEDTMP was more than 96% in 8 d, even if there was one less phosphonate group in HEDTMP than in EDTMP.

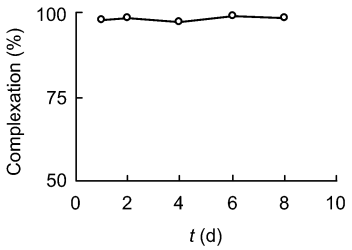

Fig.4 Stability of ^{153}Sm-HEDTMP.

3.4 ^{153}Sm-HEDTMP imaging in rabbit

Another bone-seeking radiopharmaceutical ^{153}Sm-EDTMP was prepared according to Ref. [1] and compared with ^{153}Sm-HEDTMP. About 74 MBq of ^{153}Sm-HEDTMP or ^{153}Sm-EDTMP were injected into two rabbits, respectively, and the rabbit's imaging was performed at 24 h post-injection, and so we got Fig.5 and Fig.6. The skeletal image of rabbit in Fig.5 was clear-cut and the image of non-target organs such as liver, kidney and lung was invisible. And therefore, as the same as ^{153}Sm-EDTMP, ^{153}Sm-HEDTMP must be adsorbed principally by rabbit skeleton through chemical adsorption on hydroxyapatite, the inorganic phase of bone, by the formation of O-Ca coordination bond.[10]

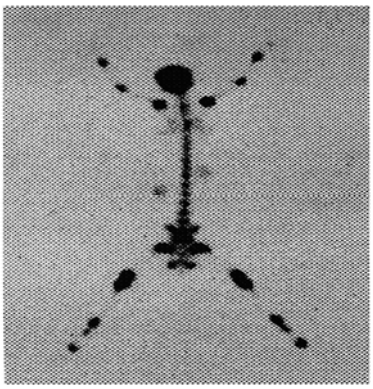

Fig.5 Rabbit skeleton image at 24 h after injection of ^{153}Sm-HEDTMP.

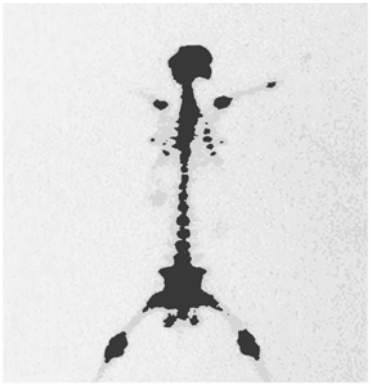

Fig.6 Rabbit skeleton image at 24 h after injection of ^{153}Sm-EDTMP.

3.5 Bio-distribution of ^{153}Sm-HEDTMP in normal mice

^{153}Sm-HEDTMP exhibited a rapid skeletal localization with a long skeletal retention. From Table 1, we saw that the bone uptake reached (17.88±1.51)%/g at 0.5 h post-injection, and was maintained at relatively high level, (17.92±1.56)%ID/g, at 48 h. Soft-tissues had relatively low activity uptake and retention, for example, the uptake of liver was (0.44±0.21)%ID/g at 0.5 h and the retention at 48 h was only (0.24±0.03)%ID/g. Table 2 gave the bio-distribution of ^{153}Sm-EDTMP. Comparison between ^{153}Sm-HEDTMP and ^{153}Sm-EDTMP indicated that two complexes all exhibited low non-target activity uptake and high bone uptake, and ^{153}Sm-HEDTMP showed higher, though not statistically, bone uptake. So the ^{153}Sm-HEDTMP had the potential to play important role in bone pain palliation radiotherapy.

Table 1 Bio-distribution of ^{153}Sm-HEDTMP in mice (n=5)

Tissues	%ID/g					
	0.5 h	1 h	3 h	6 h	24 h	48 h
Blood	2.39±0.05	0.25±0.01	0.01±0.00	0.01±0.00	0.002±0.00	0.0018±0.00
Heart	0.16±0.02	0.05±0.04	0.03±0.01	0.03±0.01	0.03±0.00	0.02±0.01
Liver	0.44±0.21	0.12±0.01	0.16±0.05	0.16±0.02	0.24±0.06	0.24±0.03
Spleen	0.52±0.01	0.04±0.01	0.05±0.020	0.04±0.01	0.05±0.00	0.06±0.00
Kidney	2.93±0.04	0.98±0.24	0.63±0.07	0.57±0.20	0.49±0.11	0.47±0.03
Muscle	0.78±0.09	0.02±0.01	0.03±0.02	0.05±0.01	0.01±0.02	0.02±0.01
Bone	17.88±1.51	25.32±3.21	25.68±1.22	20.36±1.35	18.95±1.95	17.92±1.56

Table 2 Bio-distribution of ^{153}Sm-EDTMP in mice (n=5)

Tissues	%ID/g					
	0.5 h	1 h	3 h	6 h	24 h	48 h
Blood	0.17±0.01	0..03±0.01	0.01±0.00	0.01±0.00	0.002±0.00	0.002±0.00
Heart	0.18±0.06	0.06±0.00	0.05±0.01	0.04±0.01	0.05±0.00	0.02±0.01
Liver	0.29±0.02	0.21±0.01	0.18±0.02	0.17±0.03	0.26±0.06	0.23±0.02
Spleen	0.17±0.04	0.26±0.02	0.03±0.01	0.04±0.01	0.04±0.00	0.07±0.00
Kidney	1.04±0.25	0.85±0.15	0.68±0.05	0.56±0.03	0.49±0.11	0.48±0.03
Muscle	0.34±0.04	0.10±0.06	0.04±0.02	0.02±0.01	0.01±0.00	0.02±0.01
Bone	18.60±1.21	23.37±1.15	24.12±2.88	18.23±1.12	17.05±0.71	16.56±1.01

References

1 Luo S Z, Pu M F, Qiao J *et al*. Nucl Sci Tech, 1995, **16**(3): 146-149

2 Serafini AN. Q J Nucl Med, 2001, **45**(1): 91-99

3 Berna L, Martin F, Cunill C *et al*. Rev Esp Med Nucl, 2001, **20**(2): 130-131

4 Hchum Kim S, Chen D, Muggia F. Anticancer Res, 1988, **8**: 681-684

5 McEwan AJB. Semin Radiat Oncol, 2000, **10**: 103-114

6 Crawford ED, Kozlowski JM, Debruyne FM *et al*. Urology, 1994, **44**: 481-485

7 Volkert W A, Deutsch E A. Advances in Metals in Medicine, Abrams M J eds, JAI Press, 1993, 115-149

8 Volkert W A, Hoffman T J. Chem Rev, 1999, **99**: 2269-2292

9 Luo S Z, Qiao J, Pu M F *et al*. Nucl Tech (in Chinese), 1996, **19**: 236-240

10 Jung A, Bisaz S, Fleisch H. Calcif Tissue Res, 1973, **11**: 269-280

Supported by CAEP Foundation (20020537)

Received date: 2002-07-08