In-vivo behavior of tin-radiopharmaceuticals

HE Jia-Heng, LUO Shun-Zhong, WANG Guan-Quan, YANG Yu-Qing, PU Man-Fei, LIU Guo-Ping

(Institute of Nuclear Physics and Chemistry, the Chinese Academy of Engineering Physics, Mianyang 621900)

Abstract Tin is an essential ingredient of most technetium-99m radiopharmaceuticals but its *in-vivo* distribution and long-term fate are not well understood. This work describes distribution in mice of several tin-117m labeled compounds. The results indicate that stannic-HEDTMP appears to be the best overall bone localizing agent with very low blood, muscle, kidney, or liver uptake, and its binding to bone is higher than that of tin-117m-DTPA, which make it potentially useful as an agent for skeletal scintigraphy and radiotherapy of bone tumors.

Keywords ^{117m}Sn, HEDTMP, Bone tumor

CLC numbers R817.4, O613.44

1 Introduction

Favorable radionuclidic properties of tin-117m ($t_{1/2}$ 14d; γ 159keV, 86%) make it an attractive candidate for clinical and research applications in nuclear medicine. It could be useful as a biological tracer for the study of tin metabolism and for developing tin-labeled radiopharmaceuticals for diagnostic purposes. Earlier reports have suggested the potential of tin-117m complexes for skeletal imaging and other applications. A number of compounds containing this radionuclide were studied.[1-3] Stannic compounds were found to be superior to stannous ones because of faster blood clearance and higher target/nontarget ratios. The tin-117m(4^+) labeled DTPA (diethylenetriaminepentaacetic acid) had the best combination of the percentage of bone uptake and bone-to-blood ratio.[4,5] We report here the detailed study on biodistribution of several tin-117m(4^+) labeled compounds in mice.

2 Materials

^{117m}Sn was provided by our Institute. HEDTMP, EDTMP and DTPMP were synthesized in our laboratory and the structure was confirmed by IR, m.p. and elemental analysis. Other chemicals used were of reagent grade.

3 Methods

Compounds were prepared by adding excess ligand to tin-117m(4^+). After briefly heating, the pH was carefully adjusted to 6.5~7.5. Because of the formation of semi-colloid, the solution was filtered through a sterile 0.2 μm filter. Radiochemical purity of tin-117m(4^+) labeled compounds was assessed by paper chromatography, and the labeling efficiency was ≥ 95%.

Tissue distribution studies were carried out in mice. Mice of similar age and weight were selected. 0.1 mL ^{117m}Sn-compounds were injected through tail vein. Five mice were assayed for each preparation and at each time interval. The mice were sacrificed at specific time intervals after injection, and the various organ samples in plastic vials were counted in a well-counter. The percent doses per organ for blood, bone, and muscle were weighted and calculated assuming 7, 10 and 43% of body weight, respectively, for these tissues.

The activity concentration in tissues (percent dose per gram) was normalized for 25 g body weight, using the following formula:

Percent injected dose per gram tissue
× Animal weight (g)/25.

4 Results

The normalized tissue distribution of $^{117m}Sn^{4+}$-labeled HEDTMP, EDTMP, DTPMP and DTPA in mice is shown in Table 1. The uptake's direction of every tissue is shown in Figs.1~4.

The radioactivity of ^{117m}Sn HEDTMP was almost

Received date: 2002-05-08

concentrated in bone and achieved 20% ingest quantity at 4 h post injection, whereas the highest uptake of ^{117m}Sn DTPA was only 12.72%.

Table 1 Normalized tissue distribution in mice of various $^{117m}Sn^{4+}$-labeled compounds, % injected dose/gram

Organ	Time post injection (h)	HEDTMP	EDTMP	$^{117m}Sn^{4+}$-labeled DTPMP	DTPA
Blood	1	0.0744	0.0001	1.0618	0.0024
	2	0.2328	0.0007	0.2733	0.0015
	4	0.3503	0.0012	2.2463	0.0001
	24	0.5219	0.0063	0.1564	0.0004
	48	0.3179	0.0004	0.2135	0.0000
Bone	1	13.95	17.67	22.17	8.551
	2	16.49	14.70	15.23	12.72
	4	20.20	15.32	18.04	12.29
	24	18.73	16.75	17.24	6.625
	48	19.75	11.00	17.16	5.336
Muscle	1	0.2328	0.3334	0.4051	0.0391
	2	1.1029	0.3127	0.0240	1.5937
	4	0.6064	0.2014	1.9552	0.4077
	24	0.0696	0.0122	0.2627	0.5613
	48	0.2707	0.0007	0.5577	0.0369
Liver	1	0.1925	7.5131	0.5609	0.0022
	2	0.7140	6.6667	0.7111	0.0074
	4	0.2486	7.6667	1.0754	0.0089
	24	0.3248	8.3333	1.3621	0.1042
	48	0.1346	6.6667	0.5777	0.0471
Kidneys	1	2.2139	2.6667	1.5711	0.0069
	2	3.1144	1.2011	1.1058	0.0088
	4	1.1138	1.3333	1.7.16	0.0123
	24	1.3467	1.0246	0.9296	0.0136
	48	0.4204	0.9051	0.8793	0.0077
Heart	1	0.0022	0.3333	0.3792	0.0002
	2	0.2047	0.0907	0.2269	0.0007
	4	0.1132	0.0814	0.0884	0.0008
	24	0.1451	0.0065	0.2316	0.0101
	48	0.0947	0.0008	0.3339	0.0072
Lung	1	0.4385	0.3667	1.4630	0.0045
	2	1.5110	0.0004	0.9945	0.0015
	4	0.3003	0.6667	0.7691	0.0223
	24	0.0421	0.0041	0.2126	0.3693
	48	0.0056	0.0027	0.0309	0.0352
T/NT	1	4.4225	1.5758	4.0745	154.63
	2	2.3969	1.7770	4.5659	7.883
	4	7.3922	1.5396	2.3022	27.184
	24	7.6443	1.7844	5.4643	6.2565
	48	15.877	1.4519	6.6178	39.791

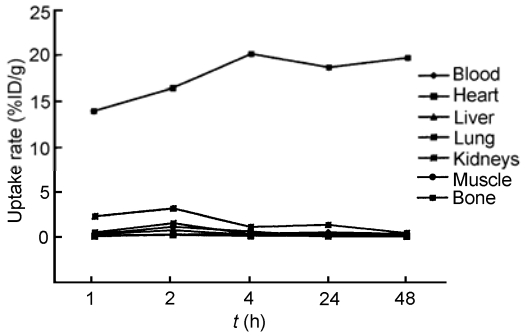

Fig.1 Tissue distribution of ^{117m}Sn HEDTMP in mice (Note: Vertical coordinate shows percent injected activity per gram of tissue; bone refers to extremity bone. The same below.)

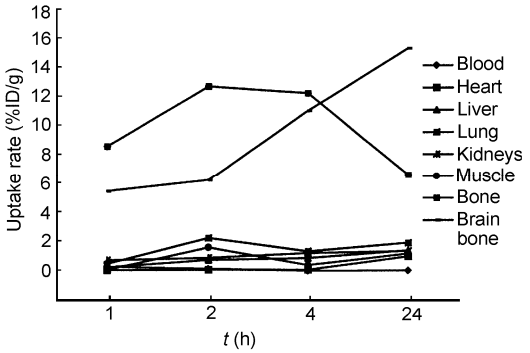

Fig.2 Tissue distribution of ^{117m}Sn DTPA in mice.

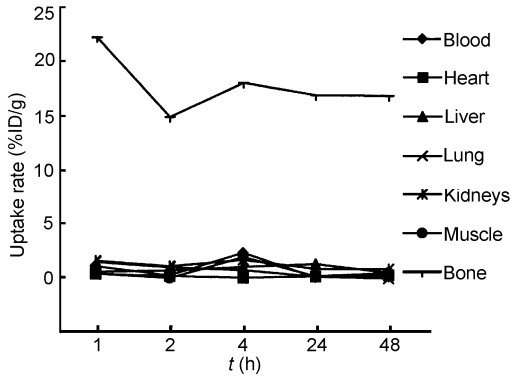

Fig.3 Tissue distribution of ^{117m}Sn DTPMP in mice.

^{117m}Sn DTPA was mostly distributed in bone (extremity bone and brain bone) of mice. But the highest ingest quantity of bone was just 15%, according to literature.[4]

After injection, ^{117m}Sn DTPMP's ingest quantity in bone was achieved 22% at 1 h. But it is a pity that it submitted to downtrend quickly. Finally only 16% remained.

From Fig.4, ^{117m}Sn EDTMP's uptake of extremity bone and brain bone is higher and the trends are relatively consistent. But *in-vitro* colloid formation leads to higher uptake of liver, going against the beamed treatment.

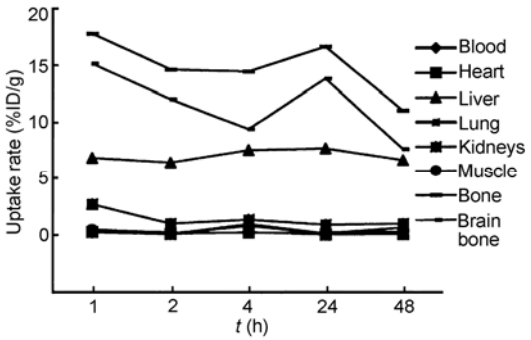

Fig.4 Tissue distribution of ^{117m}Sn EDTMP in mice.

5 Discussion

The aim of investigating newer compounds for palliative therapy of painful osseous metastases is to obtain a high concentration in abnormal bone, with a minimal effect on the red marrow. Hematologic depression has been the major adverse effect in the use of ^{32}P.[6] ^{117m}Sn is practically a pure γ-ray emitter. It is a nuclide with physical characteristics favorable for clinical and research applications in nuclear medicine. The binding of phosphate complexes of tin to bone was expected as a kind of radiopharmaceutical for palliative therapy of painful osseous metastases. Earlier study gave favorable values for the use of ^{117m}Sn(4^+)-DTPA as a therapeutic agent for pain palliation in patients with different metastases to bone.[6] In our work, several ^{117m}Sn-labeled compounds in well-defined oxidation states were prepared and evaluated in mice. The ligands include HEDTMP, EDTMP, DTPMP and DTPA. Despite the chemical differences among the ligands, high bone uptake was observed in all compounds. Substantial differences were, however, noted in the softer tissue especially liver uptake. The difference between extremity bone and brain bone uptake is particularly noteworthy. ^{117m}Sn(4^+)-HEDTMP appeared to be the best overall bone localizing agent with very low blood, muscle, kidney, or liver uptake, and the binding of ^{117m}Sn-HEDTMP to bone is higher than that of ^{117m}Sn-DTPA. ^{117m}Sn-HEDTMP may play a far more important role as a radiotherapeutic agent for bone tumors. It will probably be superior to previously

proposed agents, including the recently described ^{117m}Sn-DTPA. The in-vivo distribution of the diverse tin species as well as their long-term fate in human body, are not well known at the present time. It is necessary to make further experiments to review their behavior.

References

1 Srivastava S C, Richards P, Meinken G E *et al*. Nucl Med Biol, 1982, **2**: 1635-1638

2 Som P, Srivastava S C, Oster Z H *et al*. J Nucl Med, 1982, **23**: 78

3 Yano Y, Chu P, Anger H O. Int J Appl Radiat Isot, 1973, **24**: 319-325

4 Srivastava S C, Meinken G E, Richards P *et al*. Int J Nucl Med Biol, 1985, **12**: 167-174

5 Atkins H L, Mausner L F, Srivastava S C *et al*. Int J Nucl Med, 1995, **36**: 725-732

6 Atkins H L, Mausner L F, Srivastava S C *et al*. Radiology, 1993, **186**: 279-283