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MOLECULAR-BIOLOGICAL PROBLEMS OF DRUG DESIGN AND MECHANISM OF DRUG ACTION

BIODISTRIBUTION OF OSTEOTROPIC ^{177}LU-EDTMP – A POTENTIAL RADIOPHARMACEUTICAL FOR RADIONUCLIDE THERAPY OF BONE METASTASES

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Phosphonates labeled with beta-emitting radionuclides are widely used in nuclear medicine for palliative therapy of bone metastases. This work was aimed at studying the biodistribution of a new osteotropic antitumor agent based on *N*,*N*,*N*′,*N*′-ethylenediaminetetrakis(methylenephosphonic acid) labeled with ^{177}Lu (^{177}Lu-EDTMP) in intact animals. The biodistribution *in vivo* in intact Wistar rats of free Lu in the form of $^{177}LuCl_3$ was also investigated to assess the stability of ^{177}Lu-EDTMP. It was found that ^{177}Lu-EDTMP accumulated mainly in the skeleton (22.67 – 54.89% of the injected dose) with minimal uptake in other organs and tissues. The amount of $^{177}LuCl_3$ in bone did not significantly differ from ^{177}Lu-EDTMP uptake but the concentration of $^{177}LuCl_3$ in soft organs was significantly higher ($p < 0.05$) as compared to that of ^{177}Lu-EDTMP. The results indicated that further studies of ^{177}Lu-EDTMP in clinical application for therapy of skeletal metastases had good prospects.

Keywords: *N*,*N*,*N*′,*N*′-ethylenediaminetetrakis(methylenephosphonic acid); EDTMP; lutetium-177; nuclear medicine; osteotropic radiopharmaceuticals; biodistribution.

Bone metastases that can cause extreme pain, fractures, neurological complications, and hypercalcemia are a serious complication of many oncological diseases. Relief of pain from metastasis to the skeleton is one of the most important challenges of clinical medicine. Available methods for palliative therapy of bone pain include the use of analgesics (including narcotics), bisphosphonates, chemotherapy, and external beam therapy [1]. However, radionuclide therapy (RNT) with osteotropic radiopharmaceuticals (RPs) is most interesting because they are tolerated well and highly efficacious with simultaneous systemic action at all metastatic sites [2, 3].

Osteotropic RPs can be divided into two groups, i.e., calcimimetics and phosphonates. Calcimimetics include ^{32}P, ^{89}Sr, and ^{223}Ra, which are calcium analogs so that their *in vivo* distribution can be extremely unpredictable [3]. Phosphonates are enzyme-resistant analogs of natural pyrophosphate, possess high affinity for hydroxyapatite of bone tissue, and are widely used to design osteotropic RPs, e.g., ^{153}Sm lexidronam (^{153}Sm-EDTMP, Quadramet®), Samarium ^{153}Sm oxabiphor, etc. [4, 5].

The main problem with development of effective medicines for palliative therapy of bone pain due to metastasis of a primary tumor to the skeleton is the need to ensure delivery of an adequate dose of ionizing radiation to sites of bone metastases with minimal radiation-induced damage to bone

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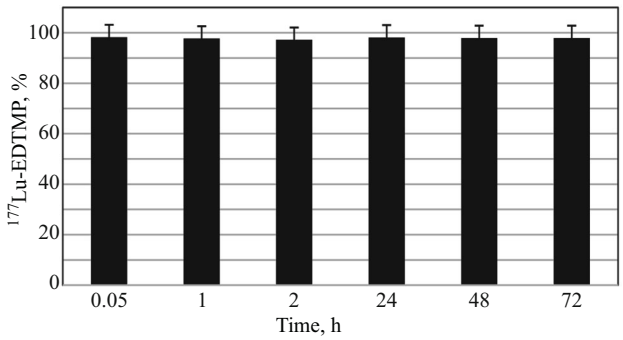

Fig. 1. Radiochemical yield of ^{177}Lu-EDTMP.

marrow. Therefore, the choice of radionuclide with the optimal nuclear-physical properties is extremely important.

Lutetium-177 (^{177}Lu) has great potential for therapeutic applications, as has been demonstrated in many works dedicated to targeted RNT of metastatic castrate-resistant prostate cancer and neuroendocrine tumors [6 – 9]. The possibility of using ^{177}Lu in practically all compound classes used for RNT is currently being studied [10]. It was proposed that ^{177}Lu could become a key therapeutic radionuclide for targeted RNT [11]. Owing to the optimal decay characteristics of ^{177}Lu [$T_{1/2}$ = 6.65 d; $E_{\beta max}$ = 498 keV (78.6%), 384 keV (9.1%), and 176 keV (12.2%); E_{γ} = 113 keV (6.6%), 208 keV (11%); and moderate penetration of soft tissues of ~0.6 mm] and the ability to produce it in medium- and high-flux research reactors, the number of which in the world is rather large, ^{177}Lu can be considered a promising radionuclide for palliative therapy of bone metastases [10, 12].

N,*N*,*N*′,*N*′-Ethylenediaminetetrakis(methylenephosphonic acid) (EDTMP) is one of the most frequently used ligands because it can form stable complexes with various radiometals (^{153}Sm, ^{177}Lu, ^{166}Ho, ^{68}Ga, etc.) [13 – 15]. This work was aimed at studying the *in vivo* biodistribution of the novel osteotropic compound ^{177}Lu-EDTMP in intact laboratory animals.

EXPERIMENTAL CHEMICAL PART

Preparation and quality control of ^{177}Lu-EDTMP. Radioactive $^{177}LuCl_3$ was obtained from State Scientific Center, Research Institute or Atomic Reactors (SSC RIAR, Dimitrovgrad, Russia). Other reagents [NaOH, HCl, NaOAc, NH_4OAc, *N*,*N*,*N*′,*N*′-ethylenediaminetetrakis(methylenephosphonic acid)] were purchased (Sigma-Aldrich, Germany).

The labeled RP was prepared by placing EDTMP (25 mg) into a 10-mL vial, adding NaOH solution (1 mL, 0.1 M), and stirring until the solid was completely dissolved. Then, the vial with the EDTMP solution was treated with sodium-acetate buffer (1.5 mL, 0.4 M, pH 4.6), stirred for 5 min, and treated with $^{177}LuCl_3$ (37 MBq, 1.0 mCi) in HCl (0.2 mL, 0.1 M). The reaction mixture was held at 95°C for 30 min, cooled to room temperature, treated with deionized H_2O (1.0 mL), and filtered through a 0.22-μm syringe filter.

^{177}Lu bound to EDTMP and free ^{177}Lu (not bound to EDTMP) were quantitatively determined by paper chromatography on Whatman-1 paper (Sigma-Aldrich, USA). The mobile phase was NH_4OAc solution (0.1 M). ^{177}Lu-EDTMP migrated to the solvent front (R_f = 0.85 – 0.95) while free ^{177}Lu remained at the origin (R_f = 0) upon elution by the mobile phase. Hydrolyzed unbound ^{177}Lu and bound ^{177}Lu were quantitatively determined by radiometric counting of the bands on the chromatography paper. The radiometry used a Wizard 2480 automated gamma-counter (PerkinElmer/Wallac, Finland).

The obtained RP was intended for intravenous injections. Radiochemical impurities in the ^{177}Lu-EDTMP RP were ≤3.0%. The pH was 4.5.

EXPERIMENTAL BIOLOGICAL PART

Pharmacokinetic studies used ^{177}Lu-EDTMP and $^{177}LuCl_3$. Solutions of ^{177}Lu-EDTMP and $^{177}LuCl_3$ were prepared immediately before biological tests.

The pharmacokinetics of ^{177}Lu-EDTMP were studied in intact female Wistar rats (160 ± 40 g). A total of 20 animals were used. They were injected intravenously (i.v.) (into a tail vein) with ^{177}Lu-EDTMP (0.1 mL, 0.37 MBq, 4.81 mg/kg of ^{177}Lu-EDTMP or 0.77 mg/rat).

The distribution of free Lu as $^{177}LuCl_3$ in intact rats (20 females) was also studied to evaluate the *in vivo* stability of ^{177}Lu-EDTMP. They were injected i.v. with $^{177}LuCl_3$ (0.1 mL, 0.37 MBq, 0.37 MBq/rat). The animals were isolated after injection of the radioactive compounds in a room specially designed for working with RPs. All manipulations with experimental animals were conducted in compliance with a handbook [16].

Animals were euthanized 5 min and 1, 3, 24, and 48 h after injection (four animals at each time point) by decapitation. Internal organs and tissues were collected. The obtained samples were placed into plastic tubes, weighed on a Sartorius electronic balance (Germany), and assayed for radioactivity. Samples (0.1 mL) of ^{177}Lu-EDTMP and $^{177}LuCl_3$ were placed into separate tubes at the time of injection for use as standards of the injected dose.

The content of ^{177}Lu-EDTMP or $^{177}LuCl_3$ per gram of organ or tissue was radiometrically assayed in percent of the injected amount (%/g) at each time point. The total content of ^{177}Lu-EDTMP and $^{177}LuCl_3$ in the skeleton was calculated considering that the rat skeleton mass was 10% of the body mass [17]. The coefficients of differential accumulation (CDA) were also calculated as the ratio of the ^{177}Lu-EDTMP or $^{177}LuCl_3$ concentration in bone to that in other organs and tissues.

TABLE 1. Concentration of ^{177}Lu-EDTMP and $^{177}LuCl_3$ in Organs and Tissues of Intact Wistar Rats After Intravenous Injection (% of Injected Dose per Gram of Organ or Tissue)

Organ or tissue	Time after injection				
	5 min	1 h	3 h	24 h	48 h
Blood	0.283 ± 0.043* 1.882 ± 0.340** $p < 0.01$	0.028 ± 0.005 1.122 ± 0.197 $p < 0.002$	0.008 ± 0.001 0.471 ± 0.037 $p < 0.01$	0.002 ± 0.001 0.011 ± 0.003 $p < 0.02$	0.001 ± 0.001 0.013 ± 0.003 $p < 0.01$
Thyroid	0.149 ± 0.026 0.541 ± 0.081 $p < 0.01$	0.065 ± 0.017 0.122 ± 0.024 $p > 0.05$	0.060 ± 0.004 0.112 ± 0.045 $p > 0.25$	0.048 ± 0.005 0.088 ± 0.011 $p < 0.02$	0.043 ± 0.012 0.045 ± 0.009 $p > 0.5$
Lungs	0.179 ± 0.021 1.022 ± 0.076 $p < 0.001$	0.028 ± 0.008 0.644 ± 0.123 $p < 0.01$	0.010 ± 0.001 0.338 ± 0.040 $p < 0.001$	0.007 ± 0.001 0.095 ± 0.010 $p < 0.001$	0.004 ± 0.001 0.075 ± 0.010 $p < 0.01$
Liver	0.071 ± 0.005 0.503 ± 0.063 $p < 0.01$	0.019 ± 0.006 0.506 ± 0.096 $p < 0.01$	0.014 ± 0.001 0.635 ± 0.037 $p < 0.001$	0.016 ± 0.002 0.326 ± 0.024 $p < 0.001$	0.016 ± 0.004 0.270 ± 0.043 $p < 0.002$
Kidneys	0.906 ± 0.148 0.521 ± 0.009 $p < 0.05$	0.159 ± 0.007 0.591 ± 0.096 $p < 0.01$	0.127 ± 0.015 0.751 ± 0.063 $p < 0.001$	0.160 ± 0.002 0.519 ± 0.051 $p < 0.001$	0.109 ± 0.026 0.425 ± 0.055 $p < 0.01$
Heart	0.060 ± 0.001 0.650 ± 0.065 $p < 0.001$	0.041 ± 0.003 0.416 ± 0.083 $p < 0.01$	0.030 ± 0.001 0.214 ± 0.023 $p < 0.001$	0.017 ± 0.001 0.063 ± 0.009 $p < 0.01$	0.011 ± 0.001 0.049 ± 0.009 $p < 0.01$
Spleen	0.052 ± 0.009 0.390 ± 0.051 $p < 0.001$	0.012 ± 0.003 0.537 ± 0.049 $p < 0.001$	0.011 ± 0.002 0.435 ± 0.041 $p < 0.001$	0.014 ± 0.001 0.306 ± 0.018 $p < 0.001$	0.011 ± 0.002 0.284 ± 0.037 $p < 0.001$
Stomach w/o contents	0.156 ± 0.021 0.253 ± 0.011 $p < 0.01$	0.030 ± 0.004 0.380 ± 0.063 $p < 0.002$	0.025 ± 0.008 0.428 ± 0.113 $p < 0.02$	0.016 ± 0.004 0.221 ± 0.036 $p < 0.002$	0.009 ± 0.003 0.202 ± 0.040 $p < 0.01$
Intestines w/o contents	0.146 ± 0.004 0.366 ± 0.071 $p < 0.05$	0.029 ± 0.001 0.372 ± 0.057 $p < 0.001$	0.019 ± 0.002 0.249 ± 0.038 $p < 0.001$	0.013 ± 0.001 0.091 ± 0.013 $p < 0.001$	0.009 ± 0.001 0.062 ± 0.011 $p < 0.01$
Thigh muscle	0.051 ± 0.006 0.202 ± 0.007 $p < 0.001$	0.008 ± 0.002 0.363 ± 0.030 $p < 0.001$	0.003 ± 0.001 0.128 ± 0.020 $p < 0.001$	0.001 ± 0.001 0.026 ± 0.004 $p < 0.001$	0.001 ± 0.001 0.034 ± 0.006 $p < 0.002$
Knee joint	1.683 ± 0.151 0.853 ± 0.052 $p < 0.01$	3.597 ± 0.609 2.862 ± 0.415 $p > 0.25$	3.460 ± 0.101 3.591 ± 0.064 $p > 0.25$	4.793 ± 0.223 5.440 ± 0.563 $p > 0.25$	3.561 ± 0.654 5.188 ± 0.563 $p > 0.1$
Femur bone	1.590 ± 0.342 0.704 ± 0.035 $p < 0.05$	2.679 ± 0.128 1.704 ± 0.050 $p < 0.001$	2.720 ± 0.133 2.649 ± 0.101 $p > 0.5$	3.758 ± 0.323 3.966 ± 0.266 $p > 0.5$	2.956 ± 0.619 3.034 ± 0.164 $p > 0.5$
Cranium	0.729 ± 0.093 0.461 ± 0.019 $p < 0.05$	1.385 ± 0.223 0.865 ± 0.050 $p > 0.05$	1.433 ± 0.050 1.270 ± 0.215 $p > 0.25$	1.561 ± 0.286 1.213 ± 0.198 $p > 0.25$	1.441 ± 0.351 1.151 ± 0.115 $p > 0.25$
Rib	1.019 ± 0.118 0.433 ± 0.095 $p < 0.01$	1.546 ± 0.142 0.879 ± 0.049 $p < 0.01$	1.712 ± 0.218 1.213 ± 0.112 $p > 0.5$	1.800 ± 0.477 1.930 ± 0.199 $p > 0.5$	1.649 ± 0.513 1.784 ± 0.090 $p > 0.5$
Spine	0.750 ± 0.084 0.538 ± 0.034 $p > 0.05$	1.459 ± 0.241 1.174 ± 0.152 $p > 0.25$	1.377 ± 0.032 1.352 ± 0.018 $p > 0.5$	1.599 ± 0.345 2.092 ± 0.354 $p > 0.25$	1.378 ± 0.348 1.853 ± 0.130 $p > 0.1$

*^{177}Lu-EDTMP
**$^{177}LuCl_3$.

The radiometric results were statistically processed using Microsoft Excel 2010 with calculation of the arithmetic means (*M*) and standard errors of the mean (*m*). Concentrations of ^{177}Lu-EDTMP and $^{177}LuCl_3$ in groups were compared using the Student *t*-criterion. Differences were considered statistically significant for $p < 0.05$.

RESULTS AND DISCUSSION

Figure 1 shows results for binding of ^{177}Lu to EDTMP. The binding of ^{177}Lu to the ligand was observed to be 98% after heating of the reaction mixture was finished. This value practically did not change for 72 h. These data were indicative of a highly stabile RP. Radiochemical impurities in the RP solution were ≤3.0% after 72 h.

The analytical results for the biodistribution found that the ^{177}Lu-EDTMP concentration was highest in bone over

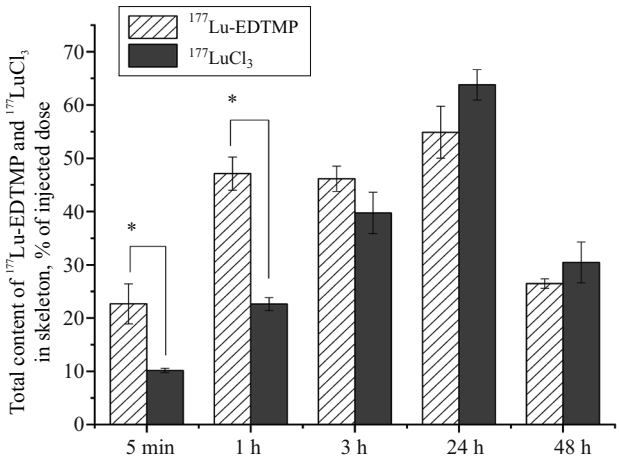

Fig. 2. Total content of ^{177}Lu-EDTMP and $^{177}LuCl_3$ in skeleton of intact Wistar rats after intravenous injection (% of injected dose); *statistically significant differences between groups ($p < 0.05$).

TABLE 2. Coefficients of Differential Accumulation of ^{177}Lu-EDTMP and $^{177}LuCl_3$ in Femur of Intact Wistar Rats After Intravenous Injection

Organ or tissue	Time after injection				
	5 min	1 h	3 h	24 h	48 h
Femur/blood	5.97 ± 1.52 0.41 ± 0.06 $p < 0.02$	104.78 ± 14.84 1.62 ± 0.09 $p < 0.001$	373.07 ± 72.17 5.68 ± 0.30 $p < 0.01$	4870.15 ± 189.35 426.62 ± 100.14 $p < 0.001$	2964.34 ± 89.38 313.25 ± 107.97 $p < 0.001$
Femur/thyroid	12.52 ± 4.17 1.39 ± 0.22 $p < 0.05$	47.17 ± 4.33 15.40 ± 2.57 $p < 0.001$	46.99 ± 4.28 35.49 ± 11.68 p > 0.25	77.83 ± 2.82 45.09 ± 4.02 $p < 0.001$	73.26 ± 9.80 68.42 ± 7.88 p > 0.5
Femur/lungs	9.26 ± 2.09 0.70 ± 0.04 $p < 0.01$	112.56 ± 16.29 2.86 ± 0.38 $p < 0.001$	275.34 ± 36.43 8.18 ± 1.01 $p < 0.001$	503.52 ± 31.10 42.84 ± 4.28 $p < 0.001$	964.24 ± 353.47 43.86 ± 8.98 $p < 0.05$
Femur/liver	23.84 ± 7.30 1.47 ± 0.19 $p < 0.05$	177.44 ± 40.50 3.66 ± 0.52 $p < 0.01$	202.80 ± 33.50 4.19 ± 0.12 $p < 0.002$	238.17 ± 24.92 12.41 ± 1.49 $p < 0.001$	207.72 ± 51.31 11.94 ± 1.58 $p < 0.01$
Femur/kidneys	1.85 ± 0.40 1.35 ± 0.06 p > 0.25	18.01 ± 2.82 3.07 ± 0.39 $p < 0.002$	21.26 ± 2.57 3.61 ± 0.35 $p < 0.001$	23.43 ± 1.81 7.76 ± 0.58 $p < 0.001$	27.38 ± 0.83 7.50 ± 1.07 $p < 0.001$
Femur/heart	26.43 ± 5.42 1.11 ± 0.12 $p < 0.01$	71.58 ± 13.59 4.48 ± 0.94 $p < 0.01$	88.44 ± 10.64 12.73 ± 1.55 $p < 0.001$	220.61 ± 28.95 66.93 ± 16.51 $p < 0.01$	271.40 ± 60.33 69.36 ± 17.45 $p < 0.02$
Femur/spleen	32.54 ± 8.89 1.90 ± 0.29 $p < 0.02$	251.23 ± 10.74 3.28 ± 0.02 $p < 0.001$	240.38 ± 45.88 6.20 ± 0.46 $p < 0.01$	267.25 ± 22.19 13.01 ± 0.58 $p < 0.001$	268.55 ± 9.67 11.21 ± 1.89 $p < 0.001$
Femur/stomach	10.11 ± 1.57 2.81 ± 0.21 $p < 0.01$	96.71 ± 15.26 4.85 ± 0.75 $p < 0.001$	140.59 ± 34.50 7.36 ± 1.50 $p < 0.01$	270.34 ± 72.28 18.80 ± 2.04 $p < 0.02$	346.82 ± 55.59 16.56 ± 2.75 $p < 0.002$
Femur/intestines	10.83 ± 2.15 2.17 ± 0.44 $p < 0.01$	98.16 ± 14.29 4.83 ± 0.52 $p < 0.001$	138.05 ± 11.59 11.64 ± 2.16 $p < 0.001$	288.65 ± 40.12 46.71 ± 7.33 $p < 0.002$	334.00 ± 100.49 56.78 ± 15.94 $p < 0.05$
Femur/muscle	32.32 ± 7.59 3.48 ± 0.12 $p < 0.01$	428.90 ± 73.63 4.80 ± 0.43 $p < 0.002$	1061.57 ± 303.62 22.45 ± 3.80 $p < 0.02$	3735.43 ± 101.64 165.20 ± 30.89 $p < 0.001$	2957.11 ± 112.06 99.49 ± 21.08 $p < 0.001$

the whole study time (Table 1). For example, ^{177}Lu-EDTMP accumulated in knee joint from 1.683 ± 0.151 %/g to 4.793 ± 0.223 %/g. The ^{177}Lu-EDTMP concentration in femur varied from 1.590 ± 0.342 %/g to 3.758 ± 0.323 %/g. The RP accumulated in other bones to ~1.5 – 2 times less than in femur. The maximum concentrations of ^{177}Lu-EDTMP in cranium, rib, and spine reached 1.561 ± 0.286 %/g, 1.800 ± 0.477 %/g, and 1.599 ± 0.345 %/g, respectively (Table 1). It is noteworthy that the maximum concentration of ^{177}Lu-EDTMP in all studied bones occurred 24 h after i.v. injection of the RP (Table 1).

The distribution of $^{177}LuCl_3$ in bones was practically the same as that of ^{177}Lu-EDTMP. The concentration of ^{177}Lu-EDTMP in bones except for spine was statistically significantly greater than $^{177}LuCl_3$ only at the initial times after injection (5 min and 1 h) (Table 1).

^{177}Lu-EDTMP was the first osteotropic RP with ^{177}Lu to be studied [18]. The radioactive label was introduced by heating $^{177}LuCl_3$ with EDTMP in a boiling-water bath for 30 min. ^{177}Lu-EDTMP accumulated primarily in the skeleton (maximum content in femur of intact rats reached 7.5%/g in 24 h) [18].

Accumulation of high levels of ^{177}Lu-EDTMP in bone was also reported in other studies [13, 14, 19 – 21]. ^{177}Lu-EDTMP was prepared at room temperature in >98% radiochemical yield in one study [14]. Rapid accumulation in the skeleton, rapid elimination from blood, and minimal accumulation in internal organs were demonstrated during biodistribution studies of ^{177}Lu-EDTMP in Wistar rats. The RP concentration in femur was 1.74 ± 0.30%/g in 3 h and reached a maximum (2.05 ± 0.48%/g) 24 h after injection [14]. It is worth noting that the time to reach the peak concentration of ^{177}Lu-EDTMP in bone (24 h) was analogous in the present work.

The biodistributions of ^{177}Lu-EDTMP and $^{177}LuCl_3$ in wild-type rats were comparatively analyzed [20]. ^{177}Lu-EDTMP rapidly accumulated in bone (~2%/g 4 h after injection), remaining practically unchanged for the next 24 h. Then, the concentration of ^{177}Lu-EDTMP in bone gradually increased (to 7%/g 7 d after injection). In turn, $^{177}LuCl_3$ also accumulated in bone, practically not differing from ^{177}Lu-EDTMP. However, high concentrations of $^{177}LuCl_3$ were observed in liver (up to 3%/g), spleen, intestines, and muscle (up to 1%/g) [20].

The total content of ^{177}Lu-EDTMP in skeleton already 5 min after injection was 22.67 ± 3.74% of the injected dose (Fig. 2). The content of ^{177}Lu-EDTMP in skeleton doubled after 1 h to 47.13 ± 3.11% of the injected dose and remained at that level (46.15 ± 2.37% of the injected dose) up to 3 h. The maximum content of the RP in skeleton occurred 24 h after injection and was 54.89 ± 4.88% of the injected dose. The total content of ^{177}Lu-EDTMP in skeleton 48 h after injection decreased to 26.48 ± 0.89% of the injected dose. The total content of $^{177}LuCl_3$ in skeleton was statistically significantly less than that of ^{177}Lu-EDTMP only 5 min and 1 h after injection while its distribution was practically the same as ^{177}Lu-EDTMP upon further accumulation (Fig. 2). The maximum content of $^{177}LuCl_3$ in skeleton reached 63.80 ± 2.87% of the injected dose 24 h after i.v. injection.

Similar contents of ^{177}Lu-EDTMP in skeleton were found before [22]. The studies used intact Wistar rats. The accumulation of ^{177}Lu-EDTMP in skeleton after 30 min was already 40.48 ± 7.48%. The total RP content in skeleton after 3 h increased to 43.50 ± 4.25%. The maximum amount of the injected dose (46.25 ± 3.48%) was noted after 24 h [22].

The biodistribution of ^{177}Lu-EDTMP prepared from a kit of reagents identical to those used to prepare ^{153}Sm-EDTMP (Quadramet®) was studied [21]. Each vial contained a lyophilized mixture of EDTMP (35 mg), NaOH (14.1 mg), and $CaCO_3$ (5.8 mg). The studies used Wistar rats. Significant accumulation of ^{177}Lu-EDTMP by bone (56.68 – 66.35% of the injected dose) was observed during 7 d after injection [21]. Moreover, accumulation of ^{177}Lu-EDTMP was found to be greater than that of ^{153}Sm-EDTMP, ^{90}Y-EDTMP, and ^{166}Ho-EDTMP [13].

The concentration of ^{177}Lu-EDTMP in internal organs and tissues was statistically significantly less than that of $^{177}LuCl_3$. The maximum content of ^{177}Lu-EDTMP in blood was 0.283 ± 0.043%/g 5 min after injection, decreasing toward the end of the study to 0.001 ± 0.001%/g. The $^{177}LuCl_3$ blood concentration was 5.5 – 59 times greater than that of ^{177}Lu-EDTMP and varied from 0.011 ± 0.003%/g to 1.882 ± 0.340%/g (Table 1).

Kidneys had the highest concentration of ^{177}Lu-EDTMP of all organs. This was due to renal excretion of labeled phosphonates, which has been reported in many works [15, 23, 24]. The ^{177}Lu-EDTMP content in kidneys during 48 h decreased from 0.906 ± 0.148%/g to 0.109 ± 0.026%/g (Table 1). Conversely, the $^{177}LuCl_3$ concentration in kidneys increased to the maximum of 0.751 ± 0.063%/g 3 h after injection, after which it decreased (Table 1).

Thyroid concentrations of ^{177}Lu-EDTMP were also characterized by lower values than $^{177}LuCl_3$. However, statistically significant differences were noted only at individual time points (5 min and 24 h) (Table 1).

The $^{177}LuCl_3$ content in other internal organs was significantly greater than that of ^{177}Lu-EDTMP. This agreed with results from studies comparing the biodistributions of ^{177}Lu-EDTMP and $^{177}LuCl_3$ [13, 20].

An analysis of the femur/internal-organs CDA data found that the ^{177}Lu-EDTMP concentration in femur was much greater than in other organs and tissues over the whole study time. This was consistent with the high numerical values of the CDA (Table 2). The maximum CDA values were recorded toward the end of the study (24 – 48 h after injection of ^{177}Lu-EDTMP).

The femur/internal-organs values for $^{177}LuCl_3$ were also greater than unity at practically all time points except for the femur/blood and femur/lungs ratios at 5 min after injection

(Table 2). However, the femur/internal-organs CDA values for $^{177}LuCl_3$ were statistically significantly less than the corresponding CDA values for ^{177}Lu-EDTMP.

Thus, ^{177}Lu-EDTMP demonstrated high affinity for bone tissue with minimal accumulation in internal organs. This was confirmed by the high femur/internal-organs CDA values at all time points. The $^{177}LuCl_3$ content in bone tissue was practically the same as that of ^{177}Lu-EDTMP although the $^{177}LuCl_3$ concentration in internal organs was significantly greater than that of ^{177}Lu-EDTMP.

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