Pharmacokinetic properties of new antitumor radiopharmaceutical on the basis of diamond nanoporous composites labeled with rhenium-188

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Abstract. Today the development of address therapeutic radionuclide delivery systems directly to tumor tissue is of current interest. It can be achieved by the design of drug containers of specific sizes and shapes from carbon-based composite materials. It will be allowed to enhance the efficacy of anticancer therapy and avoid serious side effects. In this work we studied the pharmacokinetic properties of nanodiamond nanoporous composite labeled with rhenium-188 in rats with hepatocholangioma PC-1 after intratumoral injection.
It was established that substantial part of injected radioactivity remained in tumor tissue. Within three hours after ^{188}Re-nanoporous composites injection activity in tumor constituted 79.1–91.3% of injected dose (ID). Then activity level declined to 45.9% ID at 120 hours. No more than 1.34% ID entered the bloodstream. In soft organs and tissues, except thyroid gland, the content of compound didn't exceed 0.3% ID/g. The highest activity in thyroid gland was 6.95% ID/g.
In conclusion, received results suggest ^{188}Re-nanoporous composites can be promising radionuclide delivery systems for cancer treatment.

1. Introduction

Modern technologies of cancer diseases treatment include so-called target therapy. One of its directions is the development of drug delivery systems (containers), which containing anticancer drug and/or radionuclide and acting directly on tumor cells. This approach will lead to an increase in selectivity of antitumor drugs or radiopharmaceuticals and reduce the frequency and severity of side effects. In addition, it will allow to overcome cancer drug resistance.

In this regard the various types of carbon-based materials (carbon nanotubes, nanodiamonds, fullerenes, etc.) are of particular interest due to its biocompatibility and low cytotoxicity [1 – 5]. It is

possible to synthesize composite materials with defined mechanical properties and use them to create vector nanocontainers for address drug or radionuclide delivery.

Nanodiamonds possess unique properties so they can serve as promising compounds to obtain composite materials. The structure of diamond is characterized by superior hardness, Young's modulus, high thermal conductivity and electric resistivity, as well as the low friction [6]. Each particle consists of a chemically inert diamond core and a tunable surface, which can be modified with a wide variety of functional groups. Due to these features of the surface nanodiamonds have high adsorption capacity. It is possible to receive nanoporous diamond composites from disperse nanodiamond powder and carbon matrix [7, 8]. Then durable containers containing pharmaceutical and/or radionuclide can be created. This container may be surgically placed directly into a tumor. For example, these containers with synthetic antibacterial drug levofloxacinum suppressed the development of inflammatory processes in osteal tuberculosis in chinchilla rabbits. In control group of animals treated with intravenous injection of levofloxacinum inflammatory tuberculosis continued [9]. In addition, diamond nanoporous composites allow to compensate bone defect, arising from the inflammatory process in the bone [9]. There was also shown the possibility of the composites to target drug delivery to central nervous system [10].

Rhenium-188 (17h half-life, 84% beta with 2.12 MeV maximum energy, and 16% gamma 155 keV) is one of the most convenient radionuclide for cancer therapy. One potential advantage of ^{188}Re over other radionuclides is its routine availability from the generator ^{188}W/^{188}Re during 4-6 months [11, 12]. Beta radiation causes the therapeutic effect of ^{188}Re. The short half-life of ^{188}Re can effectively reduce the system irradiation secondary to escape from the treated target. It also has a gamma-line at 155 keV allowing imaging the distribution of pharmaceuticals in the body by gamma-camera. It is expected that using carbon-based carriers labeled with ^{188}Re will lead to high levels of radioactivity directly in tumor. The present work is devoted to study of pharmacokinetic properties of diamond nanoporous composites labeled with ^{188}Re after single intratumoral injection in a PC-1 hepatocholangioma rats model.

2. Methods and materials

Nanoporous composites were developed by Gordeev S.K. in Central research institute of structural materials (Saint-Petersburg, Russia) [7] and delivered to us for further investigation. Nanoporous composites represented cylinders with the length of 2 mm and the diameter of 1 mm. The embedding of ^{188}Re was performed at room temperature. Over 99% of ^{188}Re embedded in nanoporous structure of composites after 10 min from the beginning of adsorption. The retention of ^{188}Re by nanoporous structure was higher than 99% during 48 h in a temperature range from 20 ^{0}C to 75 ^{0}C.

Biodistribution study of diamond nanoporous composites labeled with ^{188}Re was carried out in rats with hepatocholangioma PC-1. The weighs of rats were 150 ± 20 g. To get a solid version of hepatocholangioma PC-1 the donor rat with tumor was killed by cervical disruption, and the tumor tissue was isolated. Then the tumor tissue was ground up, diluted in physiological saline and implanted subcutaneously in rats. Pharmacokinetic studies were performed after 8-10 days, when the tumor volume reached 1.0-1.2 cm^3.

Each animal was implanted only one composite with activity of 0.370 ± 0.074 MBq (10 ± 2 mCi) directly in tumor. For this purpose composite was placed in needle, which was injected in the core of the tumor. Then the composite was pushed out with mandrin.

The rats were sacrificed at 5 min, 1 h, 3 h, 24 h, 48 h and 120 h (four animals at each time), their organs and tissues were isolated, placed in plastic test-tubes and weighed on electronic scales “Sartorius” (Germany). Then samples of different organs and tissues were counted in automatic gamma counter “Wizard” version 2480 (PerkinElmer/Wallac, Finland). The activity of ^{188}Re in organs and tissues was calculated as percentage of injected dose per gram (%ID/g) and per organ (%ID). The results of radiometry were presented as mean values and mean-squared errors (M ± m).

3. Results and discussion

The results of studying of pharmacokinetic properties of nanoporous composites labeled with rhenium-188 are presented in tables 1 and 2. The biodistribution data of ^{188}Re-nanoporous composites indicated high tumor retention. In fifteen minutes after injection the level of specific activity in tumor tissue was 74.3% of injected dose per gram (ID/g). Subsequently, the level of radioactivity increased and varied from 90.4% ID/g to 100.1% ID/g (table 1).

Table 1. Pharmacokinetics of ^{188}Re-nanoporous composites in rats with transplanted hepatocholangioma PC-1 after intratumoral administration (in % of injected dose per gram).

Name of organ or tissue	Time after administration					
	15 min	1 h	3 h	24 h	48 h	120 h
Blood	0,06±0,01	0,89±0,12	0,07±0,01	0,06±0,01	0,08±0,01	0,06±0,01
Thyroid gland	0,53±0,11	6,95±1,14	1,12±0,33	1,60±0,37	0,91±0,06	2,69±0,93
Lungs	0,006±0,001	0,14±0,01	0,042±0,010	0,032±0,001	0,020±0,001	0,010±0,001
Liver	0,003±0,001	0,12±0,02	0,013±0,001	0,027±0,001	0,014±0,001	0,012±0,001
Kidney	0,003±0,001	0,27±0,02	0,045±0,010	0,042±0,010	0,024±0,001	0,022±0,001
Heart	0,005±0,001	0,21±0,02	0,015±0,001	0,010±0,001	0,021±0,001	0,023±0,001
Spleen	0,002±0,001	0,12±0,02	0,011±0,001	0,020±0,001	0,014±0,001	0,009±0,001
Stomach	0,008±0,001	0,21±0,04	0,18±0,03	0,21±0,05	0,029±0,001	0,016±0,001
Muscle	0,008±0,001	0,19±0,05	0,010±0,001	0,012±0,001	0,021±0,001	0,029±0,010
Femur	0,001±0,001	0,019±0,001	0,013±0,001	0,015±0,001	0,018±0,001	0,023±0,010
Tumor	74,3±7,78	90,4±3,39	100,1±18,9	91,8±7,98	95,8±1,11	90,5±28,0
Brain	0,002±0,0001	0,083±0,010	0,005±0,001	0,006±0,001	0,010±0,001	0,006±0,001

Assessment of total radioactivity showed that during the first 3 h after injection the level of activity in the tumor was very high: from 79.1% to 91.3% of injected dose (ID). Later the content of ^{188}Re-nanoporous composits went down to 45.9% ID in 120 h (table 2).

In the blood the highest activity was just 0.89% ID/g at 1 h after injection. At the other dates the content of ^{188}Re-nanoporous composites didn't not exceed 0.06-0.08% ID/g (table 1). The peak concentration of radioactivity in blood was 1.34% ID and was monitored at 1 h after intratumoral injection (table 2).

Relatively high radioactivity concentration was found in thyroid gland (6.95% ID/g at 1 h), but remained significantly lower than that in tumor (table 1). It is known that free rhenium-188 rapidly accumulates in thyroid gland mediated by the sodiumiodide transporter [13]. So we could conclude that ^{188}Re-nanoporous composites had high stability in vivo.

Low amounts of activity were observed in other soft organs and tissues (table 1 and 2). It is an advantage of ^{188}Re-nanoporous composites as the escape of the radiopharmaceutical from the treated target can result in severe adverse events. The peak concentrations were revealed at 1 h after intratumoral injection; this corresponded with change of ^{188}Re-nanoporous composites content in blood. Some radioactivity was also detected in stomach (0.18% ID/g at 3 h; 0.21 ID%/g at 1 h and 24 h). Extremely low activity was in the brain (no more than 0.083% ID/g at 1 h). It bore evidence of ^{188}Re-nanoporous composites didn't come through blood brain barrier and didn't irradiate brain.

Table 2. Pharmacokinetics of ^{188}Re-nanoporous composites in rats with transplanted hepatocholangioma PC-1 after intratumoral administration (in % of injected dose).

Name of organ or tissue	Time after administration					
	15 min	1 h	3 h	24 h	48 h	120 h
Blood	0,74±0,12	1,34±0,18	0,98±0,15	0,81±0,10	1,00±0,07	0,85±0,17
Thyroid gland	0,012±0,002	0,19±0,03	0,029±0,007	0,044±0,011	0,022±0,001	0,041±0,011
Lungs	0,006±0,002	0,16±0,01	0,050±0,011	0,039±0,005	0,022±0,005	0,011±0,002
Liver	0,013±0,004	0,65±0,09	0,063±0,014	0,14±0,03	0,066±0,004	0,062±0,014
Kidney	0,004±0,001	0,19±0,02	0,029±0,006	0,031±0,006	0,016±0,002	0,014±0,003
Heart	0,004±0,001	0,17±0,01	0,013±0,001	0,007±0,001	0,016±0,001	0,020±0,003
Spleen	0,002±0,001	0,16±0,02	0,014±0,002	0,033±0,006	0,021±0,001	0,014±0,003
Stomach	0,010±0,001	0,26±0,05	0,24±0,02	0,27±0,08	0,034±0,004	0,020±0,005
Muscle	0,69±0,20	2,03±0,57	0,98±0,11	1,23±0,14	1,88±0,43	3,08±0,67
Femur	0,001±0,0001	0,016±0,004	0,010±0,003	0,014±0,001	0,017±0,002	0,023±0,006
Tumor	88,7±13,7	79,1±9,75	91,3±9,50	72,3±10,3	63,7±10,6	45,9±8,12
Brain	0,001±0,0001	0,14±0,03	0,010±0,003	0,041±0,005	0,059±0,006	0,044±0,009

4. Conclusion

Today the development of address therapeutic radionuclide delivery systems directly to tumor tissue is of current interest. It can be achieved by the design of drug containers of specific sizes and shapes from carbon-based composite materials. It will be allowed to enhance the efficacy of anticancer therapy and avoid serious side effects. In this work we studied the pharmacokinetic properties of nanodiamond nanoporous composite labeled with rhenium-188 in rats with hepatocholangioma PC-1 after intratumoral injection.

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In conclusion, received results suggest ^{188}Re-nanoporous composites can be promising radionuclide delivery systems for cancer treatment.

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