Original Article

Study of the Antitumor Activity of Selenium Nanoparticles

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Abstract

In the scientific literature, studies on the feasibility of using selenium nanoparticles in the development of pharmaceuticals are widely presented. The positive effects of selenium in the treatment of cancer, hepatitis C, thyroid disease, cardiovascular disease, asthma, and other diseases have been studied. This scientific paper presents the results of studies on the effect of selenium nanoparticles on the development of a cancerous tumor. The experiment was carried out on five groups of white laboratory mice, with group 1 (positive control) being healthy individuals; group 2 (negative control) - individuals infected with EPNT-5 cancer cells; group 3 (experiment) - infected individuals that received an injection of selenium nanoparticles; group 4 (experiment) - infected individuals that received an injection of selenium nanoparticles and immunoglobulin imG; group 5 (experiment) - infected individuals who received an injection of immunoglobulin imG. During the experiment, the development of the disease and the behavior of laboratory animals were monitored. After 4 weeks, blood was taken for a general and biochemical test, and the masses of the internal organs of laboratory mice were also examined.

Keywords: *Selenium nanoparticles, Cancer, EPNT-5, Immunoglobulin ImG*

Introduction

Selenium deficiency causes a large number of diseases in humans, animals, and birds.[1]. In animals and birds - white muscle disease, toxic liver dystrophy, encephalomalacia, exudative diathesis, depression, retained placenta, and pancreatic fibrosis.[2-4]

Selenium provides activity, redox enzymes, and vitamins; immunological resistance, but in addition, antioxidant protection of the body.[5-8]

Selenium is considered an essential trace element in the life of animals and humans. The positive effect of selenium in the treatment of cancer, hepatitis C, diabetes, cerebrovascular insufficiency, Alzheimer's disease, poisoning with salts of heavy metals, thyroid diseases, cardiovascular diseases, asthma, and other diseases has been more studied.[9-13] The use of selenium compounds as growth stimulants, antioxidants, and restorers of the enzymatic functions of the liver and brain is also being studied.[14, 15] It was confirmed that selenium nanoparticles are capable of exerting their action permanently, unlike antibiotics.[16-18]

Selenium nanoparticles affect biological objects at the cellular level, introducing their excess energy, which increases the effectiveness of the processes taking place in plants, i.e. are considered bioactive substances.[19-21]

It is known that with a low concentration of selenium in the body, the chance of developing oncological diseases increases.[22-24] It has been established that in areas with a higher content of selenium in the soil, the data on the incidence of cancer of the rectum, lungs, and cervix are significantly lower.[25] Moderate intake of selenium is one of the main values in maintaining the balance of expression of most selenium-dependent and selenium-independent microsomal enzymes that ensure the biotransformation of xenobiotics. Basically, selenium is the most important gene protector that blocks DNA damage by peroxidation products and metals and regulates the processes of their systemic elimination in a living organism.[26] The possibilities of using nanoparticles in the development of pharmaceutical preparations are widely discussed in the literature.

It has been studied that selenium nanoparticles show high antitumor activity,

How to cite this article: Maslyakova AR, Magomedova SA, Romantsov IN, Nurbagandov SM, Bulovin MN, Podobin OR. Study of the Antitumor Activity of Selenium Nanoparticles. Clin Cancer Investig J. 2023;12(1):43-7. https://doi.org/10.51847/yt84akUBr0

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Access this article online

Website: www.ccij-online.org

DOI: 10.51847/yt84akUBr0

Quick Response Code:

and they can act in combination with other agents for cancer chemotherapy.[27] Some mechanisms of antitumor activity have been confirmed. It has been shown that the antitumor effects of selenium nanoparticles are explained by their ability to inhibit the growth of cancer cells by inducing cell cycle arrest, inducing apoptosis, and activating autophagy.[28, 29] In addition to the original anticancer efficacy, selenium nanoparticles provide the best selectivity between normal and cancer cells.

Materials and Methods

The studies were carried out on five groups of laboratory animals (white mice). Each group included five clinically healthy individuals with standard weight and size, aged from 1.5 to 2 months.

The object of the study was laboratory animals (mice) inoculated with cancer cells (EPNT-5).

Group 1 - positive control, clinically healthy animals;
Group 2 - Negative control, cancer cells (EPNT-5) were injected subcutaneously into the withers;
Group 3 - experimental group, which received an injection with a solution of nano-selenium (0.75 mg/ml) intraperitoneally, 1 time immediately after the injection of cancer cells (EPNT-5);
Group 4 - experimental group, which received an injection with a solution of nano-selenium (0.75 mg/ml) and immunoglobulin imG intraperitoneally, 1 time immediately after the introduction of the cell line (EPNT-5);
Group 5 - experimental group, which received an injection of immunoglobulin imG intraperitoneally, 1 time immediately after the injection of cancer cells (EPNT-5).

The studies were carried out following the "Rules of Laboratory Practice in the Russian Federation" (Order of the Ministry of Health of the Russian Federation No. 708n dated August 23, 2010). Animal experiments were carried out in accordance with the rules adopted by the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.

The subject of the study was selenium nanoparticles, which were introduced to assess their antitumor activity. ImG immunoglobulin was also additionally used.

All animals were subjected to examination, which included clinical, microbiological, and laboratory studies.

Preparation and injection of cancer cells (EPNT-5)

Observing safety precautions, we centrifuge the tube with the cell line for 5 minutes at 2500 rpm, then, observing sterility, remove the supernatant to 2 ml, and resuspend the sediment without bubbles. Cell suspension with a concentration of 10^{-7} is taken into a syringe and injected subcutaneously. Groups without administration of immunoglobulin imG are administered 100 µl per animal in accordance with.[30] Groups with immunoglobulin imG are injected with 200 µl per animal.

Premedication

Before the introduction of immunoglobulin imG, premedication is carried out (Dimedrol, Analgin, and Prednisolone).

We introduce prednisolone intramuscularly 10 µl for 1 laboratory mouse, solutions of dipyrone and diphenhydramine are collected in one insulin syringe and injected 20 µl each. per animal intramuscularly, observing safety precautions.

Introduction of immunoglobulin imG

ImG immunoglobulin is administered intraperitoneally, the dose in solution at a concentration (50 mg/ml) is 100 µl. per animal at the rate of 400 mcg/kg of body weight.

Synthesis of selenium nanoparticles from dichlorodiacetophenonyl selenide

Pour 500 ml of isopropyl alcohol into a glass flask, then add 57.72 g of polyvinylpyrrolidone. We put it in the mixer at a temperature of 50 degrees. After complete mixing, 28.86 g of dichlorodiacetophenonyl selenide is added, the mixture is stirred at 1000 rpm.[31] After 40 minutes, and the resulting solution is brought to 2000 ml with distilled water.

Next, the resulting solution is put to freeze in the freezer and then sent to freeze-drying. The size of Se nanoparticles was 1-2 nm.

Preparation and introduction of a solution of selenium nanoparticles

To prepare the solution, we take 0.0175 grams of selenium nanoparticles and 10 ml of distilled water. We inject 100 µl of nano-selenium solution per mouse (intraperitoneally), which corresponds to 7 mg/kg of body weight.[32]

Equipment

During the research, the following modern equipment was used: magnetic stirrer, freeze-drying, pipette dispenser, laboratory centrifuge Sigma-202MK Refrigerated, Sigma (USA); MicroCC-20 Plus (veterinary) - automatic hematology analyzer for 20 parameters with differentiation of leukocytes into 3 populations and construction of 3 histograms; analytical balance Explorer Pro EP214C, Ohaus Europe (Switzerland); laboratory electronic scales VK-300, manufactured by CJSC Massa-K (Russia) and other devices.

Results and Discussion

During the administration of the drugs, the mice showed no visible reaction or anxiety.[33] No changes were observed within 14 days. On the 15th day of the study, formations were found in groups 2, 3, 4. In group 5, no obvious changes were observed.

Group 2 had the most pronounced formations. The dimension ranged from 0.4 to 1.6 cm in diameter. The shape is round, the borders are even and clear **(Figure 1)**.

Figure 1. Neoplasms in group 2 mice. Day 15.

In group 3, the percentage of formations was significantly less compared to the control group 2. Formations of a round shape with decorated edges. Their dimension varied from 4 to 8 mm.

Group 4 had a slightly higher percentage of education than group 3. Neoplasms had a different shapes, mostly they had a size in the range of 7-10 mm. In special cases, they reached up to 2 cm in diameter. However, the formations stood out against the background of other groups in a heterogeneous form. On day 18, education studies progressed proportionally, and evenly.

Also, one mouse from group 5 developed a neoplasm.

By the end of the experiment, it was necessary to evaluate changes in the blood and internal organs of the animals. Mice were bled by decapitation of the animal's head. After dissection, the organs were weighed, and their percentage of the total mass of animals was also compiled **(Table 1)**. Visually, in animals of group 4, the liver was paler than in other groups. A general and biochemical blood test was performed **(Tables 2 and 3)**.

Table 1. Mass of organs of laboratory mice

Indicator	Group 1	Group 2	Group 3	Group 4	Group 5
Mouse weight	29.04±1.47	25.07±9.92	28.78±2.95	26.87±1.86	**27.77±2.82**
Heart weight	0.134±0.03	0.103±0.03	0.128±0.03	0.113±0.03	**0.113±0.03**
% heart	0.459±0.1	0.427±0.08	0.445±0.09	0.421±0.08	**0.406±0.05**
Liver weight	1.16±0.21	1.44±0.51	1.28±0.16	1.38±0.05	**1.3±0.2**
% liver	4±0.62	5.8±0.46	4.45±0.35	5.15±0.52	**4.66±0.34**
Kidney weight	0.284±0.07	0.307±0.11	0.328±0.1	0.347±0.04	**0.347±0.12**
% of kidneys	0.974±0.23	1.241±0.11	1.13±0.29	1.295±0.19	**1.233±0.3**
Spleen weight	0.084±0.02	0.217±0.12	0.106±0.05	0.187±0.08	**0.11±0.02**
% spleen	**0.289±0.05**	**1.05±0.88**	**0.367±0.15**	**0.7±0.31**	**0.4±0.06**

Table 2. General blood test of laboratory mice

Indicator	Group 1	Group 2	Group 3	Group 4	Group 5
White blood cells, x10^9/L	1.26±0.61	4.37±3.53	1.02±0.35	2.17±0.8	**11.9±9.73**
Lymphocytes, x10^9/L	0.96±0.52	2.37±1.46	0.78±0.29	1.23±0.46	**11.63±9.45**
Content of monocytes, basophils, and eosinophils (MID), x10^9/L	0.28±0.11	1.6±1.58	0.2±0.11	0.57±0.17	**0.23±0.24**
Granulocytes, x10^9/L	0.02±0.04	0.37±0.52	0.04±0.05	0.1±0.01	**0.03±0.06**
Lymphocytes %	0.71±0.08	0.58±0.1	0.75±0.1	0.66±0.05	**0.98±0.01**
Content of monocytes, basophils, and eosinophils (MID), %	0.23±0.08	0.34±0.06	0.17±0.07	0.28±0.04	**0.02±0.01**
Granulocytes %	0.05±0.02	0.08±0.04	0.09±0.05	0.06±0.01	**0±0**
Red blood cells, x10^{12}/L	6.17±1.36	7.72±2.27	5.62±0.93	5.18±0.74	**4.97±0.86**
Hemoglobin, g/L	92.6±20.49	120±32.74	87.2±14.51	87±7.92	**75±15.9**
Mean corpuscular hemoglobin concentration, g/L	361.2±12.93	369±25.74	385.2±20.38	378±4.28	**383±10.45**
Mean concentration hemoglobin, pg	15.04±0.51	15.7±0.88	15.52±0.63	16.1±0.97	**15.1±0.69**
Mean corpuscular volume, fl	41.66±1.48	42.53±1.01	40.36±1.23	43.5±2.75	**39.5±1.42**
Red cell distribution width (RDW-CV), %	0.16±0.01	0.15±0.01	0.18±0.02	0.15±0.01	**0.14±0.01**
Red cell distribution width (RDW-SD), fl	33.06±3.54	31.77±2.73	35.44±2.7	32±4.02	**27.43±0.94**
Hematocrit, %	0.26±0.02	0.33±0.1	0.23±0.04	0.23±0.02	**0.2±0.04**

Platelets, x10^9/L	371.2±166.4	403.67±86.8	580±344.92	308.33±70.8	**378±88.23**
Mean platelet volume, fl	7.18±2.67	6.3±1.13	7±2.89	5.83±0.35	**5.2±0.2**
Relative width of platelet distribution by volume (PDW),fl	7.96±5.47	6.5±3.53	4.14±0.52	4.03±0.24	**4±0.49**
Thrombocrit, %	0.216±0.05	0.0025±0	0.01±0.01	0.0017±0	**0.002±0**
Percentage of large platelets (P-LCR), %	**0.15±0.2**	**0.112±0.11**	**0.14±0.21**	**0.047±0.03**	**0.008±0.01**

Table 3. Biochemical blood test of laboratory mice

Indicator	Group 1	Group 2	Group 3	Group 4	Group 5
Alanine Aminotransferase	34.52±4.09	44.07±29.72	49.64±8.5	49.27±33.08	**42.83±19.97**
Aspartate Aminotransferase	104.92±16.02	192.24±26.71	128.5±10.74	332.33±155.06	**160.03±39.91**
Creatinine	58.62±2.92	133.67±17.02	110.72±14.99	49.67±12.76	**89±55.57**
Urea	6.1±0.2	5.5±1.7	6.38±0.84	5.47±0.69	**6.67±0.33**
Phosphorus	**1.62±0.07**	**2.8±0.57**	**1.84±0.54**	**2.83±0.46**	**2.23±0.24**

Based on the data of **Tables 1-3** and observations, we can conclude that the most severe cases of the course of the disease are observed in groups 2 and 4. This indicates the depressing consequences of tumor development in animals of these groups.

At the same time, the use of selenium nanoparticles (group 3) reduces the likelihood of a cancerous tumor by 60%. The same trends were declared by Tian *et al*.[34], Stolzoff and Webster,[35] and Spyridopoulou *et al*.[36] In addition, the use of Immunoglobulin imG significantly reduces the likelihood of a tumor, which was also confirmed by Cervia *et al*.[37]

Conclusion

Over the past two decades, the direction of the use of nanoparticles in various fields has been actively developed, in particular, nanoparticles of various compositions can be used as medicinal substances. In various studies, it was found that selenium nanoparticles, unlike crystalline or amorphous selenium, can be absorbed by cells. Oncological diseases are currently one of the most important directions in the development of pharmaceuticals due to the widespread of these diseases and the lack of effective and safe therapy. We have established on laboratory animals that selenium nanoparticles 1-2 nm in size can be used as substances preventing the development of oncological diseases. As a result of the study, the following conclusions were drawn:

1. Selenium nanoparticles at a dosage of 7 mg/kg reduced the likelihood of developing an EPNT5 tumor by 60%.
2. ImG immunoglobulin reduces the likelihood of tumor development.
3. The combined use of selenium nanoparticles with immunoglobulin imG does not prevent tumor development.

Acknowledgments

The authors are thankful to the rector of North Ossetian State Medical Academy for providing a vivarium for the experiment.

Conflict of interest

None.

Financial support

None.

Ethics statement

The protocol for experiments with laboratory animals complied with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.

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