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<https://doi.org/10.24959/cphj.19.1483>**G. V. Zaychenko, O. A. Pokotylo, N. S. Nikitina***

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THE STUDY OF THE SUBCHRONIC TOXICITY OF THE CREAM WITH CERIUM DIOXIDE NANOPARTICLES IN CUTANEOUS APPLICATION IN RABBITS

The development of photoprotectors with cerium dioxide nanoparticles (CDN) for prevention of sunburns and skin cancer is expedient.

Aim. To study the subchronic toxicity of the cream with CDN in cutaneous application in rabbits.

Materials and methods. The cream with 0.25 % CDN in the doses of 0.06, 0.18, and 0.60 g/kg was applied cutaneously to Chinchilla rabbits for 90 days. The toxicity was assessed by the general state, behavior of animals, the body mass dynamics, and blood hematological and biochemical indices.

Results. The repeated cutaneous application of the cream with CDN in the doses of 0.06, 0.18, and 0.60 g/kg in rabbits did not cause significant changes in the general state and behavior of animals, consumption of food and water, the body mass dynamics, and blood hematological (hemoglobin level, erythrocyte, leukocyte, and thrombocyte count, leukogram) and biochemical (total protein, albumin, glucose, cholesterol, potassium, sodium, and chloride levels, ALT and AST activity) indices. After 1 month of application of the cream in the dose of 0.60 g/kg the glucose level was 44.5 % higher than in the intact control group, but in 3 months of the experiment differences in this parameter disappeared.

Conclusions. The data obtained concerning the safety of the cream with CDN determined the expediency of further non-clinical studies of this photoprotector.

Key words: cerium dioxide nanoparticles; subchronic toxicity; non-clinical studies; cutaneous application; Chinchilla rabbits

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Дослідження субхронічної токсичності крему з наночастинками церію діоксиду при нашкірному нанесенні кролям

Актуальною є розробка фотопротекторних засобів з наночастинками церію діоксиду (НЦД) для попередження сонячних опіків та злоякісних новоутворень шкіри.

Мета. Дослідити субхронічну токсичність крему з НЦД при нашкірному нанесенні кролям.

Матеріали та методи. Кролям породи Шиншила впродовж 90 діб нашкірно наносили крем з 0,25 % НЦД дозами 0,06, 0,18 і 0,60 г/кг. Токсичність оцінювали за загальним станом, поведінкою тварин, динамікою зміни маси тіла, гематологічними і біохімічними показниками крові.

Результати. При повторному нашкірному нанесенні кролям крему з НЦД дозами 0,06, 0,18 і 0,60 г/кг не спостерігалось значних змін у загальному стані і поведінці тварин, споживанні корму і води, динаміці зміни маси тіла, значеннях гематологічних (вміст гемоглобіну, кількість еритроцитів, лейкоцитів і тромбоцитів, лейкограма) та біохімічних (вміст загального білка, альбуміну, глюкози, холестерину, калію, натрію і хлоридів, активність АлаТ і АсАТ) показників крові. Вміст глюкози через 1 місяць застосування крему дозою 0,60 г/кг був на 44,5 % вище, ніж у групі інтактного контролю, але через 3 місяці спостереження відмінності за даним параметром були відсутні.

Висновки. Отримані дані щодо безпеки крему з НЦД обумовили доцільність проведення подальших доклінічних досліджень цього фотопротектора.

Ключові слова: наночастинки церію діоксиду; субхронічна токсичність; доклінічні дослідження; нашкірне нанесення; кролі породи Шиншила

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Исследование субхронической токсичности крема с наночастицами диоксида церия при накожном нанесении кроликам

Актуальной является разработка фотопротекторных средств с наночастицами диоксида церия (НДЦ) для предотвращения солнечных ожогов и злокачественных новообразований кожи.

Цель. Исследовать субхроническую токсичность крема с НДЦ при накожном нанесении кроликам.

Материалы и методы. Кроликам породы Шиншила в течение 90 суток накожно наносили крем с 0,25 % НДЦ в дозах 0,06, 0,18 и 0,60 г/кг. Токсичность оценивали по общему состоянию, поведению животных, динамике изменения массы тела, гематологическим и биохимическим показателям крови.

Результаты. При повторном накожном нанесении кроликам крема с НДЦ в дозах 0,06, 0,18 и 0,60 г/кг не наблюдалось значительных изменений в общем состоянии и поведении животных, потреблении корма и воды, динамике изменения массы тела, значениях гематологических (содержание гемоглобина, количество эритроцитов, лейкоцитов и тромбоцитов, лейкограмма) и биохимических (содержание общего белка, альбумина, глюкозы, холестерина, калия, натрия и хлоридов, активность АЛТ и АсАТ) показателей крови. Содержание глюкозы через 1 месяц применения крема в дозе 0,60 г/кг было на 44,5 % выше, чем в группе интактного контроля, но через 3 месяца наблюдения различия по данному параметру отсутствовали.

Выводы. Полученные данные касательно безопасности крема с НДЦ обусловили целесообразность проведения дальнейших доклинических исследований этого фотопротектора.

Ключевые слова: наночастицы церия диоксида; субхроническая токсичность; доклинические исследования; накожное нанесение; кроли породы Шиншилла

Skin malignancies are one of the most widespread types of cancer, with increasing morbidity worldwide, as well as in Ukraine [1, 2]. Melanoma, basal cell carcinoma, and squamous cell carcinoma decrease the patients' quality of life, and are the great economical burden for society [3].

Sunburn, which is an inflammatory reaction in response to acute intermittent effect of intense sunlight on the skin, is an important cancer predictor [4]. Photocarcinogenesis is induced by ultraviolet (UV) damage of DNA, inflammation and immune suppression; these effects develop directly or indirectly via reactive oxygen forms [5].

The use of photoprotective drugs and cosmetics with active pharmaceutical ingredients (API) that can absorb or reflect UV rays prevent the negative effect of sunrays on an organism [6]. Despite of wide representation on the global pharmaceutical market and proven efficacy many sunscreens have several drawbacks due to their toxicity [7, 8]. Efficacy of such products is often constrained by the ability to absorb or reflect UV rays of a limited range [9]. The search of new photoprotectors should be directed at developing products that can protect against a wide spectrum of exposure, including UV-A and UV-B.

The aforementioned factors determine an expediency of developing new effective and safe sunscreens with cerium dioxide nanoparticles (CDN) as active substances; the latter have no photocatalytic properties, possess a pronounced photoprotective and antioxidant action proven *in vitro* [10, 11].

As the use of any new nanomaterial requires multifaceted evaluation of pharmacological and toxicological properties, the safety studies of the cream with CDN designed to prevent the UV skin damage and respective malignancies are expedient.

The **aim** of the work was to study the subchronic toxicity of the cream with CDN in cutaneous application in rabbits.

Materials and methods

The cream with 0.25 % CDN developed in SSI "Institute for Single Crystals" of NAS of Ukraine was used in this study. The CDN substance with the average size of nanoparticles of 6–15 nm was synthesized by employees of LLC "NanoMedTech".

The experiment was carried out on 40 Chinchilla rabbits with the body weight of 3–4 kg and at the age of 4.0–6.0 months old according to guide-

lines [12]. Animals were kept in standard vivarium conditions at the temperature of 16–25 °C, relative humidity of 40–70 %, and free access to food and water. The quarantine period lasted for 7 days. The study groups were formed randomly.

Compliance with bioethics guidelines was verified by the expert report of the Commission in Bioethics Expertise and Study Ethics of the Bogomolets National Medical University.

Animals were divided into 5 groups with 8 rabbits in each group: 1) the intact control; 2) the group of application of the cream with CDN in the dose of 0.06 g/kg; 3) the group of application of the cream with CDN in the dose of 0.18 g/kg; 4) the group of application of the cream with CDN in the dose of 0.60 g/kg; 5) placebo – application of the cream base in the dose of 0.60 g/kg.

Creams were applied on the trimmed skin area with the size of 7×8 cm once a day for 90 days.

The toxicity was assessed by the general state, behavior of animals, consumption of food and water, the body mass dynamics, blood hematological (hemoglobin level, erythrocyte, leukocyte, and thrombocyte count, leukogram) and biochemical (total protein, albumin, glucose, cholesterol, potassium, sodium, and chloride levels, ALT and AST activity) indices.

Animals were weighted weekly for the 1st month, and then in 2 and 3 months after the beginning of the study. To determine hematological and biochemical indices blood samples were collected from the marginal ear vein before the experiment and in 1 and 3 months.

Biochemical indices were studied with the use of standard diagnostics kits for laboratories manufactured by LLC R&D enterprise "Filisit-Diagnostika". The marker hematological indices were determined on a Mythic 22 hematological analyzer (PZ CORMAY S.A., Poland).

Statistical analysis was performed on IBM SPSS Statistics v.23 (IBM, USA) and Microsoft Office Excel 2007 (Microsoft, USA) software. The paired sample t-test and ANOVA with post-hoc Tukey HSD-test were used. Differences were considered statistically significant in the case of $p < 0.05$.

Results and discussion

No negative impact on the general state or behavior of animals was observed during the experiment. Rabbits were calm; there were no differences

Table 1

The body mass dynamics of rabbits (g) after repeated cutaneous application of the cream with cerium dioxide nanoparticles (n = 8; M±m)

Body mass	Experimental groups				
	Intact control	Placebo	The cream with CDN		
			0.06 g/kg	0.18 g/kg	0.60 g/kg
Baseline	2.82±0.11	2.72±0.09	2.78±0.14	2.78±0.18	2.73±0.08
1 week	2.91±0.11	2.90±0.11	2.91±0.14	2.86±0.18	2.84±0.07
2 weeks	3.00±0.12	2.99±0.11*	3.00±0.14	3.00±0.18	2.97±0.07*
3 weeks	3.13±0.13*	3.10±0.08*	3.11±0.13*	3.10±0.18	3.06±0.08*
1 month	3.17±0.16*	3.14±0.07*	3.21±0.13*	3.21±0.16*	3.18±0.08*
2 months	3.50±0.06*	3.36±0.12*	3.50±0.10*	3.40±0.16*	3.38±0.11*
3 months	3.70±0.09*	3.60±0.14*	3.71±0.14*	3.58±0.13*	3.57±0.15*

Note. n – number of animals in the group; * – p < 0.05 compared to the baseline.

between groups in the skin and mucous membranes condition, as well as consumption of food and water. There was no loss in the body weight in the groups of application of the cream with CDN compared to the baseline and intact control (Tab. 1). In the group of the highest dose of application (0.60 g/kg) this indicator increased by 8.8 % in two weeks, while positive changes in the intact control (an increase by 11.0 %) were seen only in three weeks after the beginning of the study.

There were no differences in hematological indices between groups throughout the study (Tab. 2). In 3 months of the experiment there was a slight increase in the thrombocyte count in the groups of application of the cream with CDN in the doses of 0.06 and 0.18 g/kg (by 14.3 % and 17.1 %) compared to the baseline. However, no changes were

observed when applying the highest dose. Moreover, the aforementioned thrombocyte count values did not differ from the intact control.

The analysis of serum biochemical indices showed that the cream with CDN in repeated application did not affect the activity of ALT and AST, total protein, albumin, cholesterol, potassium, sodium, and chloride levels (Tab. 3). An increase in the serum total protein level during the experiment was observed in all groups, but the index stayed within the normal values for this species of animals [13].

When applying the cream with CDN in the doses of 0.18 and 0.60 g/kg the higher glucose level by 25.2 % and 44.5 %, respectively, was observed in 1 month of the experiment compared to the intact control group. However, by the end of the study differences in this index were absent.

Table 2

Blood hematological indices of rabbits after repeated cutaneous application of the cream with cerium dioxide nanoparticles (n = 8; M±m)

Hematological indices	Experimental groups				
	Intact control	Placebo	The cream with CDN		
			0.06 g/kg	0.18 g/kg	0.60 g/kg
1	2	3	4	5	6
Baseline					
Hemoglobin, g/l	124.6±1.2	124.8±1.7	123.6±1.0	124.2±1.9	123.0±1.1
Erythrocytes, 10 ¹² /l	5.41±0.06	5.38±0.14	5.39±0.10	5.29±0.20	5.31±0.11
Thrombocytes, 10 ⁹ /l	383.2±40.2	386.0±58.0	390.4±11.6	383.8±22.9	381.8±26.2
Leukocytes, 10 ⁹ /l	7.18±0.69	7.44±1.09	8.12±0.52	8.40±0.63	8.22±0.79
Neutrophils, %	26.20±3.77	23.20±2.22	24.40±3.67	24.80±5.22	25.80±3.29
Eosinophils, %	1.40±0.24	1.40±0.24	1.00±0.30	1.20±0.20	1.20±0.20
Basophils, %	0.40±0.24	0.20±0.20	0.20±0.20	0.40±0.40	0.40±0.40
Lymphocytes, %	71.00±3.35	74.40±1.94	73.80±3.53	72.80±4.42	71.60±3.44
Monocytes, %	1.00±0.55	0.80±0.37	0.60±0.24	0.80±0.20	1.00±0.45

Continuation of Table 2

1	2	3	4	5	6
1 month					
Hemoglobin, g/l	124.8±0.8	124.8±0.6	124.6±1.5	124.0±0.8	123.8±1.9
Erythrocytes, 10 ¹² /l	5.47±0.10	5.44±0.03	5.47±0.14	5.35±0.09	5.36±0.19
Thrombocytes, 10 ⁹ /l	404.0±25.2	402.8±29.7	397.4±32.2	401.4±24.1	397.0±27.7
Leukocytes, 10 ⁹ /l	8.86±0.63*	8.80±0.53	8.50±0.40	8.06±0.54	8.80±0.33
Neutrophils, %	27.40±3.92	25.20±1.80	25.20±1.97	26.20±3.91	27.40±1.82
Eosinophils, %	1.60±0.60	1.20±0.40	1.80±0.49	2.00±0.55	1.40±0.24
Basophils, %	0.40±0.24	0.20±0.20	0.40±0.40	0.20±0.20	0.20±0.20
Lymphocytes, %	69.40±4.27	72.60±1.50	72.00±2.12	71.20±3.73	69.80±1.69
Monocytes, %	1.20±0.58	0.80±0.37	0.60±0.24	0.40±0.24	1.20±0.58
3 months					
Hemoglobin, g/l	125.8±1.1	125.8±1.0	126.0±1.4	125.2±1.1	124.8±2.0
Erythrocytes, 10 ¹² /l	5.57±0.09	5.56±0.08	5.58±0.13	5.51±0.09	5.51±0.17
Thrombocytes, 10 ⁹ /l	425.6±24.2	418.8±30.7	446.4±24.8*	449.4±10.1*	428.6±27.1
Leukocytes, 10 ⁹ /l	9.02±0.59*	9.86±0.51*	9.16±0.50	9.06±0.62	9.42±0.46
Neutrophils, %	27.20±5.40	28.00±3.57	28.60±2.82	27.00±3.42	27.40±4.14
Eosinophils, %	1.00±0.20	1.40±0.24	1.40±0.24	1.20±0.20	1.20±0.20
Basophils, %	0.20±0.20	0.40±0.40	0.20±0.20	0.20±0.20	0.00±0.00
Lymphocytes, %	71.20±4.80	69.40±2.66*	69.20±2.40	70.80±3.01	71.00±3.90
Monocytes, %	0.40±0.24	0.80±0.20	0.60±0.24	0.80±0.37	0.40±0.30

Note. n – number of animals in the group; * – p < 0.05 compared to the baseline.

Table 3

Serum biochemical indices of rabbits after repeated cutaneous application of the cream with cerium dioxide nanoparticles (n = 8; M±m)

Biochemical indices	Experimental groups				
	Intact control	Placebo	The cream with CDN		
			0.06 g/kg	0.18 g/kg	0.60 g/kg
1	2	3	4	5	6
Baseline					
ALT, µkat/l	0.23±0.03	0.24±0.04	0.25±0.06	0.25±0.07	0.26±0.05
AST, µkat/l	0.16±0.03	0.17±0.04	0.19±0.05	0.16±0.03	0.17±0.03
Total protein, g/l	50.83±2.04	50.24±2.37	53.03±1.71	52.39±2.95	52.21±3.33
Albumin, g/l	35.03±1.90	36.22±1.96	34.22±1.39	36.02±1.26	34.53±1.72
Glucose, mmol/l	4.44±0.26	4.70±0.20	4.72±0.38	4.86±0.44	4.61±0.24
Cholesterol, mmol/l	1.28±0.08	1.38±0.18	1.40±0.10	1.32±0.23	1.35±0.16
Potassium, mmol/l	4.55±0.11	4.27±0.30	4.49±0.31	4.23±0.37	4.32±0.20
Sodium, mmol/l	160.1±11.8	167.5±9.0	164.7±6.3	176.2±11.2	163.3±11.5
Chlorides, mmol/l	106.7±3.2	105.1±3.0	104.7±2.0	105.1±1.5	102.9±1.1
1 month					
ALT, µkat/l	0.27±0.05	0.28±0.04	0.30±0.05	0.27±0.02	0.33±0.06
AST, µkat/l	0.17±0.05	0.15±0.01	0.19±0.05	0.11±0.03	0.16±0.05
Total protein, g/l	60.64±2.67*	62.78±2.04*	61.41±3.88*	66.92±4.48*	65.84±4.40*
Albumin, g/l	34.95±1.73	35.83±0.82	35.87±0.98	35.69±0.59	35.63±1.09
Glucose, mmol/l	4.45±0.11	4.72±0.42	5.12±0.59	5.57±0.81 [#]	6.43±0.24 ^{*,#,*†,§}
Cholesterol, mmol/l	1.73±0.08*	1.76±0.22	1.58±0.08	1.53±0.20	1.64±0.27
Potassium, mmol/l	4.28±0.44	4.74±0.40	4.76±0.20	4.39±0.32	4.50±0.24
Sodium, mmol/l	163.0±7.3	171.5±8.1	158.8±7.8	151.1±17.2	164.9±9.1
Chlorides, mmol/l	107.1±2.0	103.3±2.7	105.9±3.1	107.1±1.7	104.2±1.8

Continuation of Table 3

1	2	3	4	5	6
3 months					
ALT, $\mu\text{kat/l}$	0.28 $\pm$ 0.06	0.32 $\pm$ 0.03	0.38 $\pm$ 0.05	0.40 $\pm$ 0.09	0.42 $\pm$ 0.09
AST, $\mu\text{kat/l}$	0.14 $\pm$ 0.03	0.17 $\pm$ 0.08	0.19 $\pm$ 0.04	0.17 $\pm$ 0.04	0.17 $\pm$ 0.03
Total protein, g/l	70.77 $\pm$ 1.96*	74.19 $\pm$ 2.45*	73.53 $\pm$ 2.66*	70.68 $\pm$ 2.95*	74.93 $\pm$ 3.00*
Albumin, g/l	34.65 $\pm$ 0.95	35.43 $\pm$ 0.51	35.30 $\pm$ 0.91	35.92 $\pm$ 1.23	35.42 $\pm$ 1.16
Glucose, mmol/l	4.84 $\pm$ 0.32	4.22 $\pm$ 0.27	4.68 $\pm$ 0.19	4.56 $\pm$ 0.36	5.34 $\pm$ 0.67†
Cholesterol, mmol/l	2.26 $\pm$ 0.22*	2.10 $\pm$ 0.13*	1.88 $\pm$ 0.41	1.90 $\pm$ 0.32	1.91 $\pm$ 0.39
Potassium, mmol/l	4.40 $\pm$ 0.47	4.56 $\pm$ 0.39	4.31 $\pm$ 0.34	4.40 $\pm$ 0.24	4.24 $\pm$ 0.22
Sodium, mmol/l	181.1 $\pm$ 6.8*	186.2 $\pm$ 4.5*	184.0 $\pm$ 2.9*	193.2 $\pm$ 5.8	185.4 $\pm$ 3.8*
Chlorides, mmol/l	126.5 $\pm$ 2.8*	125.0 $\pm$ 3.2*	123.0 $\pm$ 2.9*	121.8 $\pm$ 2.0*	125.4 $\pm$ 2.0*

Note. n – number of animals in the group; * – $p < 0.05$ compared to the baseline; # – $p < 0.05$ compared to the intact control; † – $p < 0.05$ compared to placebo; § – $p < 0.05$ compared to the group of 0.06 g/kg cream with CDN application.

In 3 months of the experiment in most of the groups, including the intact control, a slight increase in the levels of serum sodium (by 11.2–13.5 %) and chloride (by 15.9–21.9 %) were observed. Nevertheless, there were no significant changes between the groups.

Thus, in repeated cutaneous application of the cream with CDN in the doses of 0.06, 0.18, and 0.60 g/kg for 90 days in rabbits no significant changes in the general state and behavior of animals, consumption of food and water, the body mass dynamics, and blood hematological and biochemical indices were observed.

There is literature data concerning the subacute toxicity of CDN in intragastric administration, they confirm conclusions about the safety of nanosized cerium compounds. In the experiment of A. Ramesh et al. CDN were administered to rats intragastrically in the doses of 500, 1000, and 2000 mg/kg once a day for 28 days. The authors did not observe mortality or signs of poisoning, any changes in the body mass, blood biochemical and morphological indices, mass coefficients and the structure of internal organs of animals [14].

In the study of K. Shanker et al. the subacute toxicity of CDN in intragastric administration in mice in the doses of 800, 1000, and 2000 mg/kg for 28 days was assessed. There were no pathological changes in the structure of the pancreas, kidneys, spleen, heart, and liver; no deviations in body mass,

mass coefficients of internal organs were observed, no signs of inflammation were detected [15].

CONCLUSIONS

1. In the subchronic toxicity experiment in rabbits it was found that there were no significant changes in the general state, behavior of animals, consumption of food and water, and the body mass dynamics in repeated cutaneous application of the cream with CDN in the doses of 0.06, 0.18, and 0.60 g/kg for 90 days. In the group of application of the dose of 0.60 g/kg the body mass increased by 8.8 % in two weeks, while positive changes in the intact control (an increase by 11.0 %) were seen only in three weeks after the beginning of the study.

2. No significant changes in blood hematological indices (hemoglobin level, erythrocyte, leukocyte, and thrombocyte count, leukogram) were observed in the groups of application of the cream with CDN compared to the intact control.

3. When applying the cream with CDN in the doses of 0.18 and 0.60 g/kg the higher glucose level (25.2 % and 44.5 %, respectively) was observed in 1 month of the experiment compared to the intact control group. However, by the end of the study differences in this index were absent. The analysis of serum biochemical indices showed that the cream with CDN in repeated application did not affect the activity of ALT and AST, total protein, albumin, cholesterol, potassium, sodium, and chloride levels.

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