ЕКСПЕРИМЕНТАЛЬНА ТА КЛІНІЧНА ФАРМАКОЛОГІЯ

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The experimental study of the cream with cerium dioxide nanoparticles on the model of the photodynamic injury in guinea pigs

Aim. To study the photoprotective action of the cream with cerium dioxide nanoparticles (CDN) on the model of the photodynamic injury in guinea pigs.

Materials and methods. CDN were synthesized in OOO "NanoMedTech", the cream with CDN was developed in SSI "Institute for Single Crystals" of the NAS of Ukraine. The photodynamic injury in guinea pigs was modeled with an UV-emitter. The cream with CDN was applied preventively in the dose of of 2 mg/cm^2. The erythema intensity was assessed according to S. V. Suvorov colorimetric scale, then the photoprotective activity (PPA) was calculated. The skin temperature was measured within 4 hours after exposure. The wound healing action was assessed as the number of days till complete healing of the skin of guinea pigs.

Results and discussion. The photoprotective action (PPA – 43.2 %) of the cream with CDN exceeded that of the reference drug (the cream with titanium dioxide) since the number of ulcers and deep lesions of the skin was lower. The preventive application of the cream with CDN led to the skin temperature normalization, which confirmed the ability of CDN to prevent inflammation. The wound healing action of the cream was also observed – the complete epithelization of the damaged zone took place in 5.86 days compared to 11.00 days in untreated animals.

Conclusions. The results regarding the photoprotective, wound healing action of the cream with CDN and its ability to prevent inflammation create opportunities for further study of this formulation as a photoprotector.

Key words: *cerium dioxide nanoparticles; photoprotective action; photodynamic injury*

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Експериментальне дослідження крему з наночастинками церію діоксиду на моделі фотодинамічної травми у мурчаків

Мета роботи – вивчення фотопротекторної активності крему з наночастинками церію діоксиду (НЦД) на моделі фотодинамічної травми у мурчаків.

Матеріали та методи. НЦД синтезовані у ТОВ «НаноМедТех», крем з НЦД розроблений у НТК «Інститут монокристалів» НАН України. Фотодинамічну травму мурчаків викликали УФ-опромінювачем. Крем з НЦД наносили профілактично в дозі 2 мг/см^2. Оцінку ступеня вираженості еритеми проводили за колориметричною шкалою С. В. Суворова, розраховували фотопротекторну активність (ФПА). Впродовж 4 годин після опромінення вимірювали температуру шкірних покривів. Ранозагоювальну активність визначали за кількістю діб до повного загоєння шкіри мурчаків.

Результати та їх обговорення. За фотопротекторною активністю (ФПА – 43,2 %) крем з НЦД перевищив референтний препарат, крем з титану діоксидом, на що вказувала менша кількість виразок і глибоких уражень шкірних покривів. Профілактичне нанесення крему з НЦД сприяло нормалізації температури шкіри тварин, що є підтвердженням здатності попереджати запалення. На ранозагоювальну активність крему вказувала повна епітелізація зони ураження за 5,86 діб порівняно з 11,00 у нелікованих тварин.

Висновки. Результати щодо фотопротекторної, ранозагоювальної активності крему з НЦД та його здатності попереджати запалення відкривають перспективи для подальшого вивчення даної лікарської форми як фотопротектора.

Ключові слова: *наночастинки церію діоксиду; фотопротекторна активність; фотодинамічна травма*

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Экспериментальное исследование крема с наночастицами диоксида церия на модели фотодинамической травмы у морских свинок

Цель работы – изучение фотопротекторной активности крема с наночастицами диоксида церия (НДЦ) на модели фотодинамической травмы у морских свинок.

Материалы и методы. НДЦ синтезированы в ООО «НаноМедТех», крем с НДЦ разработан в НТК «Институт монокристаллов» НАН Украины. Фотодинамическую травму морских свинок вызывали УФ-облучателем. Крем с НДЦ наносили профилактически в дозе 2 мг/см^2. Оценку степени выраженности эритемы проводили по колориметрической шкале С. В. Суворова, рассчитывали фотопротекторную активность (ФПА). В течение 4 часов после облучения измеряли температуру кожных покровов. Ранозаживляющую активность определяли по количеству дней до полного заживления кожи морских свинок.

Результаты и их обсуждение. По фотопротекторной активности (ФПА – 43,2 %) крем с НДЦ превысил референтный препарат крем с диоксидом титана, на что указывало меньшее количество язв и глубоких поражений кожных покровов. Профилактическое нанесение крема с НДЦ способствовало нормализации температуры кожи животных, что является подтверждением способности предотвращать воспаление. На ранозаживляющую активность крема указывала полная эпителизация зоны поражения за 5,86 суток по сравнению с 11,00 сутками у нелеченых животных.

Выводы. Результаты касательно фотопротекторной, ранозаживляющей активности крема с НДЦ и его способности предотвращать воспаление открывают перспективы для дальнейшего изучения данной лекарственной формы как фотопротектора.

Ключевые слова: *наночастицы диоксида церия; фотопротекторная активность; фотодинамическая травма*

Ultraviolet (UV) radiation skin damage is a widespread pathology that is observed in almost all populations. The prevalence of photodynamic injury increases in summer. A tendency towards frequent sunburns throug hout the year is observed among tanning salon attendants, persons working in the open air at high altitude, patients with some dermatological diseases, people with genetic predisposition to UV burns, and those who contact with photosensibilizing substances. The sunburn risk is inversely proportional to the level of skin pigmentation. Those who are subject to excessive UV exposure are at a high risk of melanoma, squamous cell carcinoma, and basal cell carcinoma development [1-4].

Due to UV exposure, keratinocytes start releasing cytokines and nitrogen oxide NO into the intercellular space. These substances penetrate the dermis and cause vasodilation and erythema. Apoptosis is observed in the epidermis in 1 h of insolation; the so-called "burned" cells appear. UV waves also cause degranulation of mast cells and histamine release into skin tissues. Prostaglandins E_2 and $F_{2\alpha}$ accumulate in the intracellular space of the dermis and epidermis, cause pain and hyperemia. UV irradiation also activates metalloproteinases that break down structural proteins of the dermis [2, 5, 6].

Photoprotectors of different composition are used for prevention of the photodynamic injury nowadays. Cosmetic products and drugs with "physical" filters have gained popularity recently. There is titanium dioxide (TD) and zinc oxide among them. These substances effectively reflect and refract UV waves in the spectrum that is harmful for the organism. Usually they are safe, but can have photocatalytic properties because of partial absorption of solar energy, which is a cause of the skin damage [7-9].

Cerium dioxide nanoparticles (CDN) are a new active substance with the dual mechanism of the photoprotective action. On the one hand, CDN are an effective "physical" photoprotector – a light filter, which is capable of selectively dispersing sunlight, reflecting and scattering harmful UV waves and transmitting the visible light. On the other hand, CDN are potent antioxidants, and it is an additional factor of their efficacy as a photoprotector and indicates the absence of the photocatalytic action. This double mechanism of CDN action makes them unique: they do not prevent tan, but protect against sunburns (which is not the case for the majority of modern photoprotectors). The safety of CDN was proven in the previous toxicological studies *in vitro* and *in vivo* [10-12].

The aim of the work was to study the photoprotective action of the cream with CDN on the model of the photodynamic injury in guinea pigs.

Materials and methods

CDN with the particle size of 6-15 nm were synthesized in OOO "NanoMedTech", the dermal cream with CDN was developed in SSI "Institute for Single Crystals" of the NAS of Ukraine. The photoprotective action of the cream with 0.25 % CDN was studied on the model of the photodynamic injury in guinea pigs [13] – acute photodynamic skin inflammation (UV erythema) caused by an OKN-011M UV-emitter (Zavet, Ukraine). The irradiation range was 220-400 nm. The efficacy of the cream with CDN was compared to the reference drug – the cream "Biocon SPF 40" with TD as an active substance.

Experiments were carried out on 40 outbred guinea pigs of both sexes with the body mass of 450-500 g. Guinea pigs were divided into 4 experimental groups, 10 animals each: group 1 – intact animals, group 2 – animals with the untreated photodynamic injury (radiation-exposed animals), group 3 – animals that received the cream with CDN prior to UV exposure, group 4 – animals that received the cream with TD prior to UV exposure.

The study was carried out in accordance with conditions of the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

Prior to the beginning of the experiment all animals underwent depilation of the region of the back, which was divided into three smaller regions of 3 cm^2 each.

The UV irradiation source was positioned at 10 cm away from the skin surface, the exposure time was 3 min, which corresponded to 5 MED (minimal erythema doses).

The creams were applied in the prevention regimen on the depilated skin regions of guinea pigs 20 min prior to UV exposure in the dose of 2 mg/cm^2, the dose was chosen in compliance with the international recommendations [7]. Each animal from group 3 received a topical dose of 0.1 mg/kg of CDN.

A degree of erythema intensity was measured in points (from 0 to 4) 1, 2, 4, 8, 16, and 24 h after UV exposure according to S. V. Suvorov colorimetric scale: 0 – the absence of erythema, 1 – mild erythema (rose skin tone), 2 – moderate erythema (rose-red skin tone), 3 – profound erythema (red skin tone), 4 – severe erythema (bright red skin tone). For each animal the arithmetic mean was measured based on 3 cm^2 regions on the back [14].

The photoprotective action (PPA) of creams was calculated by formula:

$$PPA = (E_{co} – E_{cr}) \times 100 / E_{co},$$

where: E_{cr} – is the degree of erythema intensity (points) on the skin region where the cream was applied (groups 3, 4), in 24 hours after exposure; E_{co} – is the degree of erythema intensity (points) on the skin region underwent UV irradiation (group 2 – radiation-exposed animals), in 24 hours after exposure.

To assess the degree of the UV tissue injury within 4 hours after exposure the temperature of the skin surface was measured [15]. It is an integral index of the inflammatory process activity and a marker of vascular changes in the dermis in the case of UV irradiation. An increase in temperature manifests itself due to release of proinflammatory and vasoactive mediators, such as histamine, serotonin, bradykinin, prostaglandins, and interleukins [16, 17]. The measurement of the temperature of the animal skin folds was carried out with a MT1931 thermometer (Microlife, Switzerland).

The process of wound healing in guinea pigs was recorded every day in the same time starting from the moment when UV irradiation completion, and it was measured in the number of days to complete recovery. The criteria of complete recovery were epithelization of the irradiated region, the complete absence of ulcers, bleeding, and other visible lesions of the epidermis and dermis.

The statistical processing of the experimental data was performed with the IBM SPSS Statistics v.23 software (IBM, USA) using two-sample t-test assuming equal variances for independent samples and paired sample t-test for dependent ones. Differences were considered statistically significant at $p < 0.05$.

Results and discussion

The dynamics of the erythema development in guinea pigs was assessed by the degree of erythema intensity during the experiment (Tab. 1). An increase of the parameter was seen in radiation-exposed animals throughout the study (24 hours). Areas with severe erythema and skin wounds were observed in these guinea pigs.

The less serious injury was seen in animals received the cream with CDN prior to UV exposure. The degree of erythema intensity was 88.9 % lower in this group compared to radiation-exposed animals after 1 hour of the experiment. PPA of the cream with CDN was 43.2 %.

In animals that received the cream with TD (the reference drug) prior to UV exposure the photodynamic injury was also less pronounced than in radiation-exposed animals (pathology). The degree of the erythema intensity was 77.8 % lower in 1 hour of the experiment. However, the efficacy of the cream with TD was inferior to the one of the formulation studied. More ulcers were observed on the skin of guinea pigs that received the reference drug compared to animals treated with the cream with CDN, and the area of injury was also larger. In animals that received the cream with CDN prior to UV exposure the degree of the erythema intensity was 55.6 % and 46.2 % less in 2 and 4 hours of the experiment, respectively, compared to the group of the preventive use of the cream with TD. PPA of the reference drug was 32.4 %.

Thus, the cream with CDN showed a pronounced photoprotective action and was not inferior to the reference drug. There was less number of ulcers and deep lesions on the UV exposed regions of the skin of guinea pigs in the group of the preventive use of the cream with CDN compared to the group of animals that received the cream with TD. The area and intensity of the photodynamic inflammatory process, which main element was erythema, were smaller in the group of animals received the cream with CDN prior to UV exposure.

Table 1

The dynamics of the erythema development in guinea pigs with the photodynamic injury and in the group of animals received the cream with CDN prior to UV exposure (n = 10; M ± m)

Groups	Degree of erythema intensity, points					
	1 hour	2 hours	4 hours	8 hours	16 hours	24 hours
Intact	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Radiation-exposed (pathology)	1.80 ± 0.25*	2.20 ± 0.25*	2.80 ± 0.25*	3.30 ± 0.26*	3.60 ± 0.16*	3.70 ± 0.15*
Radiation + the cream with CDN (mg/cm^2)	0.20 ± 0.13*/**	0.40 ± 0.16*/**/***	0.70 ± 0.15*/**/***	1.40 ± 0.27*/**	1.80 ± 0.20*/**	2.10 ± 0.18*/**
Radiation + the cream with TD (2 mg/cm^2)	0.40 ± 0.16*/**	0.90 ± 0.23*/**	1.30 ± 0.26*/**	1.80 ± 0.25*/**	2.10 ± 0.23*/**	2.50 ± 0.27*/**

Note: n – the number of animals in the group; * – $p < 0.05$ compared to intact animals; ** – $p < 0.05$ compared to radiation-exposed animals; *** – $p < 0.05$ compared to animals received the cream with TD prior to UV exposure.

Table 2

The dynamics of the skin temperature changes in guinea pigs with the photodynamic injury and in the group of animals received the cream with CDN prior to UV exposure (n = 10; M ± m)

Groups	Skin temperature, °C			
	Baseline	1 hour	2 hours	4 hours
Intact	36.900 ± 0.084	36.920 ± 0.051	36.870 ± 0.067	36.910 ± 0.028
Radiation-exposed (pathology)	36.900 ± 0.037	37.850 ± 0.040*/****	38.100 ± 0.061*/****	37.440 ± 0.043*/****
Radiation + the cream with CDN (2 mg/cm^2)	36.940 ± 0.040	37.150 ± 0.037*/**/***/****	37.030 ± 0.033*/**/***/****	36.950 ± 0.031**/***
Radiation + the cream with TD (2 mg/cm^2)	36.880 ± 0.033	37.940 ± 0.059*/****	37.380 ± 0.070*/**/****	37.110 ± 0.043*/**/****

Note: n – the number of animals in the group; * – $p < 0.05$ compared to intact animals; ** – $p < 0.05$ compared to radiation-exposed animals; *** – $p < 0.05$ compared to animals received the cream with TD prior to UV exposure; **** – $p < 0.05$ compared to the baseline.

Regarding the skin temperature the values were physiological in intact animals (Tab. 2). In radiation-exposed guinea pigs starting with the 1-st hour of the experiment and onwards, the temperature increased compared to intact animals and the baseline values. In 4 after exposure the value increased by 0.54 °C.

In 4 hours of the study the skin temperature normalized in animals received the cream with CDN prior to UV exposure, which was indicative of the ability of the formulation studied to prevent inflammation.

The reference drug was less efficacious than the cream with CDN. The skin temperature in guinea pigs in 1, 2, and 4 hours of the experiment was by 0.79, 0.35 and 0.16 °C higher, respectively, compared to the group of animals that received the cream with CDN. No normalization of the parameter was observed; the skin temperature remained increased after application of the cream with TD and UV exposure throughout the interval studied.

The time of complete epithelization of the skin of animals was studied in order to determine the wound healing action of the cream with CDN (Tab. 3). The complete wound healing was observed in all guinea pigs. The process was more rapid in the group of animals that received the cream with CDN (by 46.7 %) than in radiation-exposed animals. The preventive application of the formulation studied reduced the time to complete epithelization of the skin by 1.88-fold. The data obtained confirm the photoprotective and wound healing action of the cream with CDN.

In animals that received the reference drug the complete epithelization of the skin was 36.4 % faster than in untreated guinea pigs. The differences of this parameter were not statistically significant for groups of application of both creams.

Table 3

The time of complete epithelization of the skin of guinea pigs with the photodynamic injury and in the group of animals received the cream with CDN prior to UV exposure (n = 10; M ± m)

Groups	Time of complete epithelization, days
Intact	0
Radiation-exposed (pathology)	11.00 ± 0.90*
Radiation + the cream with CDN (2 mg/cm^2)	5.86 ± 0.86*/**
Radiation + the cream with TD (2 mg/cm^2)	7.00 ± 0.76*/**

Note: n – the number of animals in the group;
* – $p < 0.05$ compared to intact animals; ** – $p < 0.05$ compared to radiation-exposed animals.

CONCLUSIONS

The cream with CDN in the preventive use in the dose of 2 mg/cm^2 on the model of the photodynamic injury in guinea pigs has exhibited the photoprotective action (PPA – 43.2 %). It exceeds the reference drug (the cream with TD) by the photoprotective action due to less degree of the erythema intensity – lower number of ulcers and deep lesions of the skin. Normalization of the skin temperature was indicative of the photoprotective action of the cream with CDN and its ability to prevent inflammation, while in animals that received the cream with TD prior to UV exposure the higher values (by 0.16-0.79 °C) were observed throughout the experiment.

The cream with CDN revealed the wound healing action. There was the complete epithelization of the skin of guinea pigs within 5.86 days of the experiment, it was faster by 46.7 % than in the group of animals with the untreated photodynamic injury, for which the value was 11.00 days.

The cream with CDN showed better photoprotective action than the reference drug as indicated by less severity of the photodynamic injury and normalization of the skin temperature.

The results obtained create opportunities for further study of the cream with CDN as a photoprotector with the wound healing action and the ability to prevent inflammation.

Conflict of Interests: authors have no conflict of interests to declare.

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